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THE ROLE OF THE SYMPATHETIC NERVOUS SYSTEM IN ACUTE POLIOMYELITIS

PRELIMINARY REPORT

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THE purpose of this paper is (1) to describe clinical observations of the sympathetic nervous system involvement in acute anterior poliomyelitis, (2) to record briefly the presumptive evidence, (3) to present conclusive evidence that angiospasm exists in the acute stage of poliomyelitis and may be responsible for muscle spasm and pain, and (4) to suggest practical methods for relief of pain and spasm.

CLINICAL OBSERVATIONS OF SYMPATHETIC NERVOUS SYSTEM INVOLVEMENT

A. In the Cervical Region.—Paralysis of the cervical sympathetic is either extremely rare or else it is mistaken for facial paralysis, and is classified, therefore, as polioencephalitis. Since 1928 we have seen three such cases. The muscle paralyses were different in each case. However, the symptoms relating to Horner's syndrome were the same: ptosis, or narrowing of the palpebral fissure; enophthalmos, or retraction of the eyeball; contraction of the pupil on the affected side; flushing of the face due to the dilatation of the blood vessels; and anhidrosis, or absence of sweating.

B. In the Thoracic Region.—The thoracic portion of the sympathetic may be diseased; the symptoms in this condition, being mainly visceral, are less easily recognized.

Our patient with thoracic sympathetic involvement was a boy aged 14 years, well developed and well nourished, who suddenly complained of occipital headache. On the following day the headache spread to the temporal regions. The temperature rose to 101° F. The family doctor diagnosed the condition as "grippe." The next morning the patient was unable to support his head or flex his forearms. The diagnosis was then changed to poliomyelitis and he was admitted to the Kingston Avenue Hospital.

Physical examination: On admission to the hospital the temperature was 101° F., pulse 120. The heart sounds were irregular; there were no murmurs.

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The chest revealed wheezes and rhonchi on auscultation, but no fine râles. There were no dull areas on percussion. His face was cyanotic. A blotchy purplish macular eruption was noted on the chest and shoulders. He was dyspneic.

Neurological examination: There was no evidence of cranial nerve involvement. The arches of the soft palate were symmetrical; the uvula was in the midline; the soft palate moved freely. The tongue on protrusion deviated neither to the left nor to the right and was freely movable. There was no stagnant mucus about the pillars, and none on the posterior pharyngeal wall. He did not cough. His voice was clear and he pronounced the consonant *B* sharply and distinctly. He drank fluids and swallowed semisolid food without difficulty. Respirations were shallow and rapid and occasionally they were deep and slow. The alae nasi dilated with inspiration. The diaphragm moved freely and the abdominal reflexes were present. His neck was not stiff. He was unable to flex his forearms and could not support his head. He was mentally clear, cooperated willingly, but was frightened. His eyes were wide open. His face was cyanotic, his lips were cherry red, and he perspired profusely. He had one complaint, "I cannot get my breath."

From the clinical picture it was evident that this patient had neither bulbar poliomyelitis nor respiratory muscle paralysis. However, because of the extreme cyanosis and shortness of breath, the admitting physician placed him in the respirator. He showed marked improvement in the respirator for a short period of time. The cyanosis cleared, the lips became pink. However, he did not synchronize with the machine and had to be taught to do so. He tried very hard to breathe with the respirator but failed. His face soon became cyanotic and his lips dark red. He continued to complain that he could not get his breath. It was evident that he was suffering from hypoxia. Something was preventing the oxygen from reaching the red cells in the blood. The respiratory tract was investigated. The patient was laryngoscoped and the vocal cords were seen to move freely; there were no polyps, ulcers, nor edema about the larynx. The patient was examined bronchoscopically and no mucus plugs either in the trachea or bronchi were seen. Roentgen examination showed the lung fields to be clear. On the assumption that he had bronchiolar spasm, the patient was given epinephrine subcutaneously without any response. Having failed to discover an obstruction in the laryngotracheobronchial tract, the patient was given oxygen by mask without results. Oxygen by nasal catheter at the rate of 10 to 15 L. per minute was substituted. The oxygen thus delivered apparently failed to reach the blood for his face remained cyanotic and he continued to complain that he could not get his breath. The temperature rose to 104° F. and the pulse dipped to 90. He became comatose and died thirty-six hours after admission, with oxygen flowing through the catheter into the bronchial tree.

We felt that the cause of death in this case was probably due to spasm of the pulmonary blood vessels. Purves Stewart[1] regards the vasoconstriction of the pulmonary vessels, with the transient dilatation and irregularity

of the right heart met with in certain gastric and hepatic disorders (and seen by us in this case of poliomyelitis), as an affection of the thoracic portion of the sympathetic nervous system.

The clinical picture of pulmonary angiospasm very closely simulates the signs and symptoms of bulbar poliomyelitis and sometimes the patient is tracheotomized unsuccessfully.

C. In the Gastric Region.—Sympathetic nervous system involvement either directly or reflexly may produce transient vomiting for which no explanation can be found. The vomiting may begin with the onset of poliomyelitis or during the first few days of the disease. Repeated lumbar punctures do not offer any relief. This vomiting is probably due to a transient pylorospasm.

D. In the Intestinal Region.—Involvement of the sympathetic nervous system may manifest itself either by constipation or diarrhea. Most of our patients were constipated and required attention in the form of frequent enemas. Grulee and Panos[2] met with similar experiences. However, Ivan Wickman[3] states that in his series of cases diarrhea was more common than constipation. The stools may be watery, green, and fetid. Spastic constipation with its hard, dry stools, and also mucous colitis with its paroxysms of increased peristalsis accompanied by an excessive secretion of intestinal mucus, are probably both evidences of vagotonus. The apparent contradiction in ascribing constipation and diarrhea to the same cause is explained by the fact that in one condition the circular fibers of the intestine are affected, producing constipation, while in the other the longitudinal fibers are affected, causing diarrhea.

E. In the Rectal Region.—Some of our patients showed evidence of chronic intestinal obstruction as a result of sphincter spasm. Their abdomens became distended both by gas and feces and assumed barrel-like shapes. Rumbling and gurgling were heard and felt. The feces had to be removed mechanically from their rectums.

F. In the Bladder Region.—Sympathetic nervous system involvement may disturb the normal function of the bladder. The bladder has a double innervation, partly from the sympathetic and partly from the parasympathetic. The sympathetic reflex center is situated in the lateral horn of the spinal cord in the region of the third, fourth, and fifth lumbar vertebrae. The parasympathetic nerves reach the bladder via the second, third, and fourth sacral roots. Involvement of the sympathetic nerves causes increased tonus of the sphincter and dilatation of the bladder with retention of urine. Involvement of the parasympathetic nerves produces relaxation of the sphincter and contraction of the bladder or incontinence of urine. Bladder involvement is not uncommon when both lower extremities are paralyzed. Retention of urine seems to be more common than incontinence. Twenty-two patients in our series had retention of urine and only one had incontinence.

G. In the Skin.—Involvement of the sympathetic nervous system in the skin may reveal itself in different ways:

1. Profuse sweating: Sweating is an early sign and can be found in nearly all poliomyelitis cases. Sometimes the patients continue to perspire for weeks

after the acute phase has subsided. There seems to be no relationship between the height of the temperature and the sweating.

2. Tache spinale: While stroking the skin to elicit abdominal and cremasteric reflexes we occasionally noticed: (a) the appearance of a pink streak which in some cases would fade within three to five minutes; (b) when muscle weakness or sluggish reflexes were present the streaks would assume a purple hue and remain up to ten minutes; or (c) not infrequently the streaks would appear cyanotic and would linger up to one-half hour before they would fade into normal skin color. The length of time required for the cyanotic tache to fade impressed us very much. It was evident that there was interference in the blood circulation to the part in question.

3. Angioparesis in the skin: Skin eruptions have been observed during the first few days and sometimes later in the disease. The exanthemas may be vesicular, resembling chicken pox but lacking the red areola about the vesicle, or morbiliform, resembling measles, but lacking the coryza, cough, and Koplik spots. Occasionally the rash is scarlatinaform. Here, differential diagnosis is almost impossible, since the patient has a red throat, temperature, headache, and vomiting, symptoms common to both poliomyelitis and scarlet fever. The Schultz-Charlton test is always negative, but this, however, does not rule out scarlet fever. The onset of paralysis or paresis establishes the diagnosis of poliomyelitis.

4. Angiospasm in the skin: The Schick test on a paralyzed upper extremity may manifest itself within twelve to twenty-four hours in the form of intense redness with vesiculation. The vesicles may be either confluent or discrete. Occasionally a single large bulla appears. This bulla may rupture and leave a sloughing base. Healing is very slow and takes as long as two to three months. This indolence may be the result of angiospasm, which condition diminishes the blood supply to the tested area and hence fails to remove the toxin causing the sloughing area.

PRESUMPTIVE EVIDENCE THAT SYMPATHETIC NERVOUS SYSTEM INVOLVEMENT MAY PRODUCE ANGIOSPASM

A.—Medicine has long accepted the thesis that the cyanosis, muscle spasm, and pain of Raynaud's disease, and the cyanosis and cramplike pain in intermittent peripheral arterial claudication are due to angiospasm.

B.—The chronic poliomyelitic extremity with its cyanosis and muscle spasm and tenderness behaves and responds like the extremity of Raynaud's disease.

C.—External application of heat, in all probability, produces vasodilatation both in the chronic poliomyelitic extremity and in the extremity of Raynaud's disease. The improved circulation to the limbs may be responsible for the improved color, feeling of warmth, and diminution of pain and muscle spasm.

D.—The same results were obtained by White and Smithwick[4] by denervating the spastic blood vessels of the lower extremities of five cases of old poliomyelitis by preganglionic sympathectomy. The blood circulation returned to the extremities. These patients were followed for one year, and the results were reported as very good.

From 1937 to 1947 inclusive, 1,172 acute poliomyelitis patients were admitted to the Kingston Avenue Hospital. Approximately 90 per cent showed evidence of pain and muscle spasm in varying degrees. Six hundred seven, or 51 per cent, developed evidence of anterior horn lesions. Of these, fifty-one died, or 4.25 per cent. Five hundred fifty-six, or 47.5 per cent, were transferred to orthopedic hospitals. Five hundred sixty-five, or 48.25 per cent, were discharged free of neurological symptoms after one- to three-weeks' stay in the hospital.

Since 51 per cent of the acute poliomyelitis patients develop anterior horn lesions or muscle paralysis, and 90 per cent show evidence of pain and muscle spasm, it follows that the sympathetic nervous system may be more responsive to irritation as compared to the central nervous system, hence expressing itself more often, even in the mildest infections. The manner in which it appears to express itself is angiospasm causing ischemia resulting in muscle tenderness and spasm.

CONCLUSIVE EVIDENCE THAT ANGIOSPASM EXISTS IN THE ACUTE STAGE OF POLIOMYELITIS

The neuropathology of the spinal cord in poliomyelitis suggests that an inflammation of the anterior horn cells automatically involves the lateral horn in which the sympathetic nerves have their origin. It is reasonable to assume that the lateral horn pathology may be either mild, moderate, or severe. The mildest form expresses itself in ordinary edema. Ivan Wickman[5] states that the edema is of no slight importance from the clinical point of view as it affords a plausible explanation for the rapid disappearance of the neurological signs. Therefore, as soon as the edema subsides in the lateral horn, the angiospasm is released and muscle tenderness and spasm disappear. This is what happens in the patient who recovers in one to three weeks. When the lateral horn is severely damaged the resulting angiospasm may be permanent. The affected extremity may become cold, clammy, and cyanotic.

David Bodian and Howard A. Howe[6] studied the route of transmission of the virus from the portal of entry to the central nervous system. They state that the evidence indicates that the virus migrates peripherally and that the intensity of the lesions of the peripheral ganglia corresponds relatively well to the intensity of the lesions in the adjacent central nervous system. It is of great interest that Sabin and Ward[7] were able to demonstrate virus in the abdominal sympathetic plexus of one case of poliomyelitis, thus indicating at least one pathway of centripetal virus propagation.

We have repeatedly noted lateral and posterior horn involvement in addition to lesions in the intermediate zone similar to those described by Peters.[8] In a few cases we secured portions of the cervical sympathetic chains for histologic examination. It was no surprise to us that we found edema of the ganglia to be present in addition to small foci of infiltration of the ground substance. Very striking in some cases were the degenerative changes in many ganglion cells. Ganglion cells appeared shrunken and nuclei were obscured or absent. In some, coarse basophilic granules were seen in the cyto-

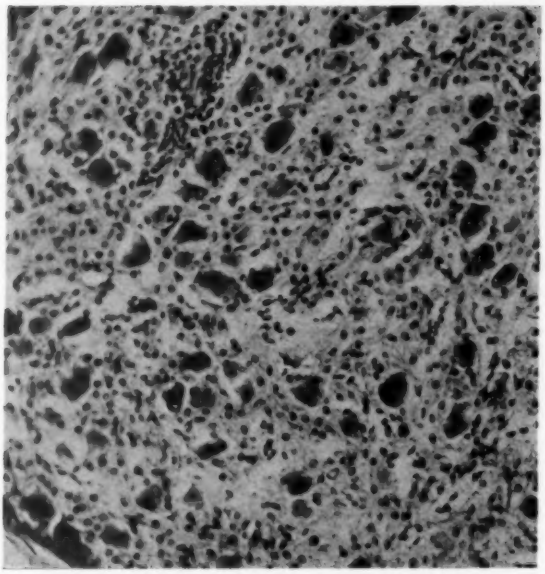

Fig. 1.—Section of sympathetic ganglion in a case of bulbar poliomyelitis, showing round cell infiltration of stroma. (Hematoxylin and eosin stain, ×200.)

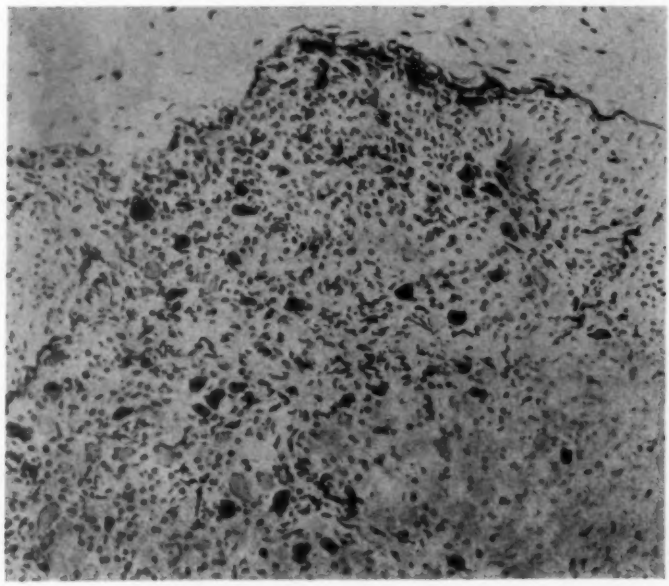

Fig. 2.—Section of sympathetic ganglion in a case of bulbar poliomyelitis showing degenerative changes in ganglion cells. Nissl preparation. (Hematoxylin and eosin stain, ×200.)

plasm; nuclear-cytoplasmic distinction was unclear in some cells, and in others the nucleoli appeared fragmented. Distinct neuronophagia in the sympathetic ganglia was not seen, leading us to the belief that the changes were probably reversible. From our anatomic observations, it was not difficult to explain the functional insufficiency of the sympathetic nervous system as manifested in the clinical observations noted. Steindler[9] has described similar changes.

In 1947 Collens, Foster, and West[10] reported fifteen convalescing poliomyelitis patients treated with paravertebral sympathetic block. Oscillometric recordings were made at the ankles only. Readings made prior to injection gave an average excursion of 1.5. Post block recordings in all patients were increased. Pain, muscle spasm, and tenderness were completely relieved in three patients. All others benefited greatly.

While clinical and therapeutic findings established that angiospasm did exist in the chronic paralytic extremity of poliomyelitis, evidence had to be found to show that a similar condition was present during the acute stage. The oscillometer, therefore, was used to test vascular expansion in all extremities, both paralyzed and nonparalyzed, in acute anterior poliomyelitis. Since emotional disturbances and undue body activity distort the oscillometric readings, and complete cooperation was necessary for accurate findings, we chose twelve patients, mostly adolescent and older, for this study.

Chart Illustrating Oscillometer Readings.—Six of the twelve patients studied had one or more extremities paralyzed. The oscillometric excursions were well below the average normal, not only in the paralyzed extremities but in the nonparalyzed as well.

One patient had weakness of back muscles but no evidence of paralysis in the extremities. The oscillometric excursions revealed that the blood vessels in the extremities were in spasm.

Another patient had back muscle spasm and no detectable evidence of paralysis in the extremities. The oscillometric excursions indicated angiospasm in the extremities.

Three patients had no evidence of paralysis on admission and none during the stay in the hospital. The only neurological findings were muscle tenderness and spasm. The oscillometric excursions on the extremities were well below the average normal, thus showing that the blood vessels were not expanding.

The last patient in this study revealed a left facial paralysis and hence polioencephalitis was diagnosed. There was no evidence of any other paralysis anywhere in the body. We decided, on general principles, to test the vascular expansion in the lower extremities and, to our surprise, we found the blood vessels in spasm.

In the lower extremities where the oscillometric readings were very low the dorsalis pedis as well as the anterior tibial pulse was very weak or hardly obtainable. We did not correlate the degree of vasospasm with the degree of muscle spasm or the intensity of the pain. It would appear, however, that the greater the spasm in the blood vessels the more marked the ischemia in the muscles and the more severe the muscle spasm and hence the pain.

TABLE I

NO.	AGE (YR.)	SEX	CLINICAL DIAGNOSIS	SPINAL FLUID		INVOLVEMENT					OSCILLOMETRIC READINGS									
											AVERAGE NORMAL EXCURSIONS									
											THIGHS		BELOW KNEES		ABOVE ANKLES		ARMS		FOREARMS	
											RT.	LT.	RT.	LT.	RT.	LT.	RT.	LT.	RT.	LT.
											7	7	6	6	4	4	7	7	7	7
											ACTUAL EXCURSIONS									
											THIGHS		BELOW KNEES		ABOVE ANKLES		ARMS		FOREARMS	
						EXTREMITIES														
				CELLS	TOTAL PROTEIN	RU.	RL.	LU.	LL.	OTHER	RT.	LT.	RT.	LT.	RT.	LT.	RT.	LT.	RT.	LT.
1	21	F	P.P.*	166	78	x‡	x	0§	0	—	1½	1½	4	2	1½	1½	2½	2½	2	2½
2	18	M	P.P.	380	†	x	0	0	0	—	1	1½	2	3	2	1½	4	4½	2½	2
3	15	M	P.P.	72	210	x	x	0	x	—	5	3	3½	3½	2	1½	4½	4½	2½	2
4	18	M	P.P.	34	90	0	x	0	x	—	1½	1¼	4	4	3	4	—	—	—	—
5	9	F	P.P.	18	260	0	x	0	x	—	1½	1	2½	1	2	1½	3	1½	1½	1
6	7	F	P.P.	285	72	0	x	0	x	Back	0	0	½	¼	½	¼	½	2	—	—
7	11	M	P.P.	151	79	0	0	0	0	Weak back	2	1	1	2	1	1¼	2	2	1	1
8	13	M	P.P.	255	60	0	0	0	0	Weak back	2	2½	2½	3	1½	1½	3	1½	1½	2
9	13	F	N.P.†	210	40	0	0	0	0	—	½	1¼	1½	1½	1	½	1½	1½	1	1
10	11	M	N.P.	178	—	0	0	0	0	—	2	2½	½	2½	2	1½	2	2	2	2
11	6	M	N.P.	131	60	0	0	0	0	—	2	1½	1¼	2	1	1	3	3½	2	1½
12	8	M	Polio. Enceph.	97	38	0	0	0	0	Left facial	2½	2½	5½	3½	1¼	1¼	—	—	—	—

*P.P., Paralytic poliomyelitis.
†N.P., Nonparalytic poliomyelitis.
‡X, Paralysis.
§O, No paralysis.

METHODS FOR RELIEF OF PAIN AND SPASM

Having convinced ourselves that the blood vessels were in spasm in the acute stage of poliomyelitis and that the ischemia might be responsible for the muscle pain and spasm, we set out to relieve the angiospasm by mechanical means.

Since hot packs were introduced for the relief of muscle spasm and pain, we have steadily looked for a more pleasant and less laborious method to replace it. Short wave diathermy produces clean, comfortable, controlled heat which is easily tolerated. We introduced it to an extremity showing angio- as well as muscle spasm with pain. After treating the extremity for a short period of time the muscle relaxed and the pain diminished or subsided. To bring more blood to a spastic muscle, a rhythmic constrictor was introduced to assist the dilated blood vessels in supplying blood to the ischemic muscle. Quicker and better results were obtained. The muscles relaxed and the pain diminished or subsided, only to return when the artery or arteriole went back into spasm.

Both hot packs and short wave diathermy produce vasodilatation with relief of muscle pain and spasm. Both methods require trained personnel and are very expensive.

We therefore decided to use vasodilator drugs by mouth. We chose nicotinic acid as the vasodilator and gave it in doses of 100 mg. This drug dilated the nonspastic blood vessels and showed no effect on the spastic blood vessels. The patient would either become flushed or state that he felt warm in the nonparalytic areas and cold in the paralytic areas; thus showing that the drug would not dilate the spastic blood vessels.

At this time our patients were transferred to orthopedic hospitals and our experiment terminated. At the same time Graubard, Robertazzi, and Peterson[11] reported 140 patients treated with intravenous procaine. They classified their cases (1) traumatic, (2) inflammatory, and (3) miscellaneous.

> "In the miscellaneous cases we found some interesting phenomena. We did not expect to find any changes in the neurologic cases, but treated them in order to see if any improvement could be noted. In two cases of anterior poliomyelitis, with flaccid paralysis of many years' duration, there was the following response: during the infusion the patients stated that a tingling sensation of warmth crept down the affected extremities. This vaso-dilatation was maintained following each injection for several days and even weeks. This prompted us to try procaine infusions in two cases of spastic anterior poliomyelitis. The results were relief of spasm, increased mobility and improved muscular control. From our observations, the use of intravenous procaine in alleviating muscle spasm suggests its therapeutic application in the symptom relief of the distress of acute anterior poliomyelitis.[12] The use of curare in conjunction with physical therapy has given some very satisfactory improvement. The use of procaine intravenously in patients who have been on curare therapy every eight hours for one month with only slight improvement and relaxation of the spasticity, responded with what might be termed a dramatic response."

SUMMARY

We have presented clinical evidence showing that sympathetic nervous system involvement in acute poliomyelitis may manifest itself in the cervical region by Horner's Syndrome, in the thoracic region by spasm of the pulmonary blood vessels with dilatation and irregularity of the right side of the heart, in the gastric region by pylorospasm, in the intestinal region by constipation or diarrhea, in the rectal region by intestinal obstruction, in the bladder region by retention or incontinence of urine and in the skin by angioparesis or spasm.

Presumptive evidence has been presented to show that the blood vessels in the chronic poliomyelitic extremity behave and respond similar to the angiospasm of Raynaud's disease or the cramplike pain in intermittent peripheral arterial claudication.

Conclusive evidence that the blood vessels were in spasm was found in the twelve patients tested with the oscillometer. The actual excursions were far below the normal. We have also shown that angiospasm was present in the encephalitic, paralytic, and in the nonparalytic extremity of acute poliomyelitis. Pathologic evidence to substantiate the clinical findings was presented by showing involvement of the lateral horn as well as of the sympathetic ganglia.

We have demonstrated that short wave diathermy with the rhythmic constrictor dilated the blood vessels and increased the blood supply to the extremity. The muscles relaxed and the pain diminished or subsided only to return when the blood vessels contracted.

However, we feel that neither short wave diathermy nor hot packs are the solution for the relief of the muscle spasm and pain in acute poliomyelitis, since these methods do not produce sustained vasodilatation. The method of choice would be a drug that could be administered by mouth, subcutaneously, or by the intravenous route.

We fully understand that the subject matter in this paper is debatable. We hope, however, that it will provoke others to investigate further the role of the sympathetic nervous system in acute poliomyelitis, and that it will eventually lead to a better understanding of the clinical picture of the disease and hence to a more scientific therapeutic approach.

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12. Arrangements have been made to use Procaine intravenously on a selected group of acute poliomyelitis cases during the summer of 1948. The results will be reported as soon as the study is completed.

HISTOPLASMOSIS IN CALIFORNIA CHILDREN

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CURRENT textbooks[1-3] describe histoplasmosis as a highly fatal disease rarely diagnosed before autopsy. The invading organism, *Histoplasma capsulatum*, is a fungus which in the tissues resembles protozoal bodies and produces a clinical picture somewhat similar to kala-azar.

A severe infection is characterized by irregular fever, anemia, leucopenia, emaciation, and cough. There may be enlargement of the lymph nodes, spleen, and liver, and ulcerations in the gastrointestinal tract.

The fungus apparently usually enters through the mouth but also has been described as entering through a cutaneous ulcer. Autopsy findings most frequently describe enlargement of mesenteric lymph nodes and extensive ulceration of the intestinal mucosa. Pulmonary invasion described in the fatal cases was thought to be part of the generalized disease and not the primary infection.

SOURCE OF INFECTION

Histoplasma capsulatum survives the action of gastric juice in experimental infection of dogs.[4]

The organism has not been found in nature but has been isolated from dogs, which raises the question of domestic pets as carriers.

INCIDENCE (AGE AND SEX)

Histoplasmosis has been described as occurring at any age from three months to seventy years with 28 per cent below age 13 years.[1-3] Among adults there were three times as many male as female patients with less disproportion among children (one and one-half times as many cases in boys as girls).

The U. S. Army reported cases among whites, Negroes, Japanese, Chinese, and Filipinos.[1] No occupation studies have appeared.

SYMPTOMS

The first studies in 1906 by Darling[5] described histoplasmosis as a chronic disease characterized by fever, emaciation, anemia, leucopenia, and splenomegaly with a duration of three weeks to eight months. Later studies recognized other aspects such as involvement of skin and mucous membranes especially about the nose and mouth.

In children there is an insidious onset with loss of weight, fever, gastrointestinal disturbances, and coughing. The liver, spleen, and lymph nodes show enlargement. Mesenteric lymphadenitis and enlargement of the hilar lymph nodes are almost always reported at autopsy. The supposition is that these follow ulceration of the bowel and dissemination to the lungs. (Involvement of the bone marrow sometimes produces anemia and leucopenia.) Lymphocytosis is usually found in children.

Lesions in the lung are composed of multiple small foci widely distributed. They may be pleural or subpleural and often cause pleurisy-like pain. There may be râles in the bases but otherwise physical examination of the chest is negative.

X-RAY FINDINGS

The usual picture shows enlargement of hilar lymph nodes, peribronchial thickening, and multiple miliary calcifications.[6]

These residual calcifications after infection with histoplasmosis have not been shown to have any clinical significance. The same is true of coccidiomycosis which is caused by a related organism.

MYCOLOGY

The organism belongs to the fungus family of Endomycetes which is the chief mold group identified as causing disease in man.[7]

Another fungus in this same family classification is *Coccidioides immitis*.

Histoplasma capsulatum is primarily a parasite of the reticuloendothelial system[8] and is demonstrated in the macrophages. Extracellular forms have rarely been found and in this respect it differs from all other pathogenic fungi.

The fungus when demonstrated in peripheral blood or from a biopsied lymph node appears as small oval bodies within the large mononuclear cells. An oval body measures 1 to 5 microns and has a thick capsule. On culture media this yeastlike form buds and mycelia grow. The fungus produces distinctive chlamydospores which are smooth, thick-walled, and tuberculated.

From 1906 to 1937 only thirteen cases were reported in the literature. Many more have been reported since then.

Within the last two years studies have shown that histoplasmosis is not necessarily a fatal disease but that it is apparently benign or even subclinical in many aspects.

Christie and Peterson[9] at Vanderbilt University reviewed the problem of calcification occurring in the chests of children who were not sensitive to tuberculin.

From many sections of the United States there was reported a high incidence of pulmonary calcification in young people who had repeatedly negative tuberculin skin tests.

For example, Gass and his associates[10] studied 1,167 school children in Tennessee with serial x-rays and skin tests over a four-year period. They found 83 per cent of white children and 72 per cent of Negro children had pulmonary calcifications and negative tuberculin tests. This was a local phenomenon.

Other studies showed the incidence of pulmonary calcification was forty times as high in Tennessee as in Alabama.[6] Since calcified lesions in the chest had always been considered tuberculosis in the past, the specificity of the tuberculin skin test was sharply questioned.

After Dr. Charles E. Smith[11] of Stanford had demonstrated that coccidioidomycosis produces a primary complex which goes on to calcification indistinguishable from that of tuberculosis, Christie and Peterson did routine skin testing of children in Tennessee with coccidioidin and histoplasmin. They

found a very high correlation between pulmonary calcification and positive histoplasmin reactions. Coccidioides was not a factor in their study.

Large-scale skin-testing programs were carried out in other geographical areas, i.e., Ohio, Kansas, and Michigan, where pulmonary calcifications were found in tuberculin negative persons.[12, 13]

The conclusions were reached that (1) a mild or even subclinical form of histoplasmosis was responsible for a high proportion of calcifications seen in x-rays of tuberculin negative reactors; (2) the greatest prevalence of this phenomenon was found in the area of the eastern slope of Mississippi River Basin. Supporting these conclusions, a geographical pattern of cases of disseminated miliary calcifications emerged from the Selective Service induction x-rays. These showed the highest incidence to be among men from the lower Mississippi River Basin.

SKIN TESTING

The preparation used in skin testing is histoplasmin 1:100 dilution, 0.1 c.c. applied intradermally. Tests are read in seventy-two hours. This time is selected because skin-test sensitivity to histoplasmin is reported to rise sharply at forty to sixty hours and to remain present for two to three weeks. A positive reaction consists of edema surrounded by a large area of erythema. The diameter of the area of induration must be 5 mm. or over to be considered a positive test. Slight desquamation usually follows. There is neither induration or erythema in a negative test.

The significance of a positive histoplasmin test is like the tuberculin test in being a satisfactory exclusion test in subacute and chronic forms of the infection.

The specificity of the test is not as good in experimental animals as in man, but continued studies indicate that reactions observed are truly allergic phenomena related to antecedent infection. There is some cross sensitivity with blastomycin.[14, 15]

Special tuberculin luers and needles should be used for all testing to avoid adsorption on syringes.

Following Dr. Christie's reports of mild and subacute cases of histoplasmosis in children in the South, it seems reasonable to suppose that mild infections with this fungus may occur in other sections of the country.

With this possibility in mind the author skin-tested a series of eighty-five children in California who had suggestive clinical symptoms. In every case the histoplasmosis-testing was done with material supplied by Dr. Christie and followed the technique described above.

For the tuberculin testing P.P.D. was used, 0.1 c.c. intradermal of No. 1 followed by 0.1 c.c. of No. 2. Brief case reports of children with positive histoplasmin and negative tuberculin skin tests are presented.

CASE REPORTS

CASE 1.—Jimmy aged 6½ years.

Past History.—The child was born in Boston but lived for two years in Texas and Arizona. He had scarlet fever at the age of 3 years followed by recurrent bronchitis. For the past two years he has coughed at night.

Presenting Complaints.—Great fatigue, loss of weight, nightmares, evening temperature 100-101° F., and night cough.

Physical Examination.—A pale, listless child who was eight pounds underweight for his body build. Positive findings included anterior and posterior cervical lymphadenitis, posterior pharynx granular, and occasional râles in the chest.

Laboratory Findings.—Red blood cells 3.6 million to 3.9 million, hemoglobin 10.15 to 11.95 Gm., white blood cells 7,100 to 12,000, polymorphonuclears 36 to 42 per cent, lymphocytes 62 to 54 per cent, eosinophiles 3 to 6 per cent, sedimentation rate 30 to 11 mm. fall per hour, stomach washing negative for tubercle bacillus.

Skin Tests.—Tuberculin, three negative reactions in ten months. Coccidioidin negative. Histoplasmin violently positive, area of erythema 5 × 6 cm. with indurated center at seventy-two hours, followed later by mild desquamation.

X-ray Chest.—Shows multiple miliary calcifications in the parenchyma (see Fig. 1).

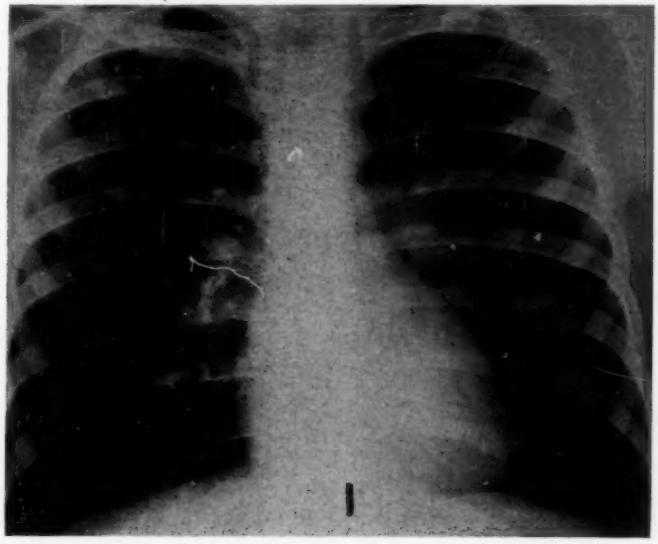

Fig. 1.

CASE 2.—Bruce aged 5½ years.

Past History.—This child was born in California and went to Texas for two years while his father was stationed there in military service. Soon afterward when the family returned to California the boy started to cough and this continued for eight months.

Presenting Complaints.—Chronic cough, worse at night; loss of weight and failure to gain; irritability; apprehension, fatigue, and occasional bouts of elevated temperature.

Physical Examination.—A hypertonic, overactive boy who was five pounds underweight for his body measurements. Tonsils were moderately hypertrophied and pitted; cervical lymph nodes were palpable and no râles were heard in his chest.

Laboratory Findings.—Blood count and sedimentation rate were within normal limits.

Skin Tests.—Tuberculin negative. Coccidioidin negative. Histoplasmin positive.

X-ray Chest.—Shows multiple hilus gland enlargements and multiple discrete calcium deposits far out in the parenchyma both sides (see Fig. 2).

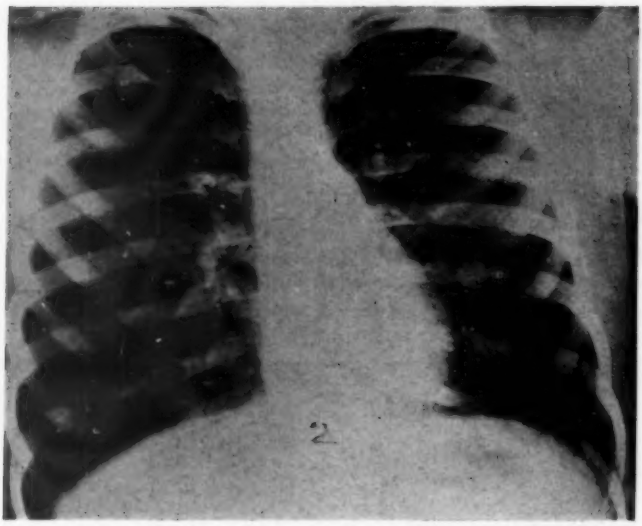

Fig. 2.

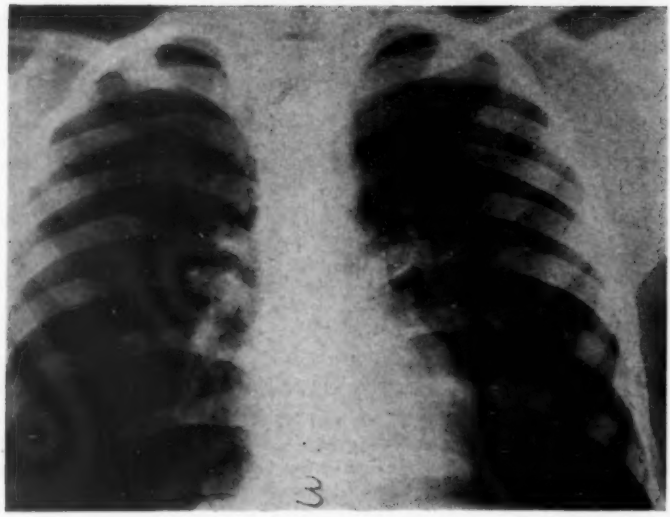

Fig. 3.

CASE 3.—Walter aged 7 years.

Past History.—The boy was born in San Francisco and has lived near there all his life except for one visit to Missouri of one month duration. He has had recurrent attacks of asthma and is sensitive to a number of pollens and epidermals.

Presenting Complaints.—Sharp, stabbing precordial pain produced by deep breathing, fatigue with great languor, and afternoon temperature of 100-100.8° F.

Physical Examination.—Pale, slow-moving boy with satisfactory nutritional status. Tonsils hypertrophied and cryptic, cervical glands enlarged and tender. Shallow breathing but no friction rub noted. Rather diffuse tenderness over right lower quadrant to deep palpation.

Laboratory Findings.—Red blood cells 4.2 million, hemoglobin 12.85 Gm., white blood cells 6,050, polymorphonuclears 23 per cent, lymphocytes 55 per cent, eosinophiles 16 per cent, monocytes 6 per cent; sedimentation rate 22 mm. fall per hour. Electrocardiogram normal for age.

Skin Tests.—Tuberculin negative. Histoplasmin positive, 3 × 3 cm. followed by desquamation.

X-ray Chest.—Shows multiple miliary calcifications with several lymphatic courses back to the hilus nodes (see Fig. 3).

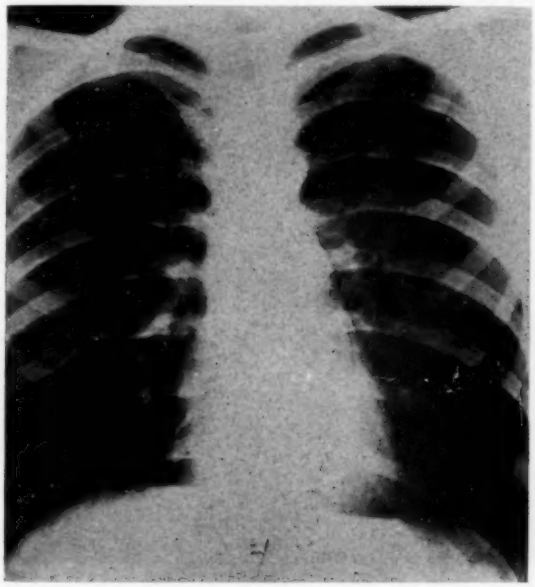

Fig. 4.

CASE 4.—Barbara aged 11 years.

Past History.—This child has lived most of her life in Wyoming and came to California two years ago.

Presenting Complaints.—Nonproductive cough and draining ear for duration of four months, recurrent attacks of asthma and urticaria, evening temperature.

Physical Examination.—Emaciated-looking girl with very droopy posture who was twelve pounds underweight for her body build. She had posterior cervical lymphadenitis, a sour smelling discharge from her left ear, a few high pitched asthmatic râles in both lung bases, and moderate tenderness over her right lower quadrant on palpation of the abdomen.

Laboratory Findings.—Red blood cells 4.1 million, hemoglobin 11.82 Gm., sedimentation rate 12 mm. fall per hour. Aspergillus found in smear from ear.

Skin Tests.—Tuberculin negative. Histoplasmin positive, 2 × 3 cm. with induration.

X-ray Chest.—Shows enlarged hilus glands and several small calcifications especially on the right side (see Fig. 4).

CASE 5.—Sally aged 9½ years.

Past History.—This girl, born near San Francisco, has never been away from home farther than one hundred miles. She has had pneumonia twice and recurrent attacks of asthma. In infancy she was allergic to wheat, eggs, and milk.

Presenting Complaints.—Intermittent fever usually in the evening, dry cough, worse at night, duration 18 months; headaches, pyelitis, and loss of weight.

Physical Examination.—Droopy, emaciated-looking girl who is thirteen pounds underweight for her build. Cervical lymph glands were hard, shotty, and not tender. The mucous membranes of her nose and throat were pale and she had a few fine moist râles in her chest. Lymph nodes in her right groin were palpable and so was her spleen.

Laboratory Findings.—Red blood cells 3.95 million, hemoglobin 10.95 Gm., white blood cells 7,300, polymorphonuclears 36 per cent, lymphocytes 51 per cent, eosinophiles 12 per cent, monocytes 1 per cent, sedimentation rate 17.9 mm. fall per hour.

Fig. 5.

Skin Tests.—Tuberculin negative. Histoplasmin positive. Coccidioidin negative.

X-ray Chest.—Shows rather massive hilar enlargement on both sides with multiple discrete pulmonary calcifications in the parenchyma. There are many lymphatic courses back to the hilar nodes (see Fig. 5).

SUMMARY

A review of the current status of histoplasmosis is presented.

The probability of wide-spread infection of a mild or subclinical form of histoplasmosis is pointed out.

Case histories are summarized on five children with multiple pulmonary calcifications all of whom are tuberculin-negative and histoplasmin-positive to intradermal skin tests.

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CUSHING'S SYNDROME IN CHILDREN

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INTRODUCTION

IN 1932 Harvey Cushing[1] separated from a welter of case reports on polyglandular dyscrasias a group of patients with a common clinical picture. This syndrome, which is now associated with his name, was thought by Cushing to be a manifestation of hyperactivity of a basophilic adenoma of the pituitary gland. He suggested the term basophilism. In the light of subsequent investigations his original thesis as to pathogenesis has not been substantiated; nevertheless, the syndrome he described has been generally accepted as a clinical entity.

Albright[2] has summarized the cardinal clinical features of Cushing's syndrome as follows:

(a) Diabetes which is usually mild and often only demonstrable as an unresponsiveness to an alimentary hyperglycemia (i.e., decreased sugar tolerance), but which is resistant to insulin.

(b) Muscular weakness with a low creatinine as indicative of decreased muscular mass.

(c) Osteoporosis, especially of the spine (not to be confused with osteitis fibrosa generalisata or with osteomalacia, since the serum phosphatase level is normal rather than high), associated with hypercalcinuria early in the disease, and, in many instances, with nephrolithiasis.

(d) A thin, reddish (?transparent) skin, easy bruisability, often large purplish striae, and a marked susceptibility to skin infections.

(e) Impotence in men and amenorrhea in women.

(f) Mild to moderate obesity with a tendency for the fat to be deposited in the neck and face ("moon-face") and to spare the extremities.

(g) Mild hirsutism without other evidence of virilism (clitoris not enlarged, thyroid cartilage and voice normal in female patients) usually but not always associated with a slight to moderate elevation in the urinary excretion of the 17-ketosteroids.

(h) Mild erythrocytosis (red count circa 5.8 million) without increased blood volume.

(i) Hypertension and arteriosclerosis, often accompanied by coronary disease and vascular disease of the kidneys.

LITERATURE

Prior to and subsequent to Cushing's article describing the symptom complex and postulating its relationship to hyperactivity of the basophilic cells of the pituitary, sporadic case reports appeared describing a similar syndrome in

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association with hyperplasia or a neoplasm of the adrenal cortex. Cushing was well aware of the frequent occurrence of histologic evidence of overactivity of an adrenal cortex, but felt that the adrenal changes could be explained on the basis of pituitary stimulation, as there were other examples of changes in distant tissues initiated by the pituitary.

Crooke,[3] in 1935, made a fundamental observation in respect to the pathology of basophilism or Cushing's syndrome. He demonstrated characteristic hyaline changes or peculiar areas of degranulation in the basophile cells of the pituitaries in twelve patients with typical clinical pictures. As a rare chance finding this change was found to a minor degree in nine out of 350 control pituitary glands. In those control patients in which the change was found, it was not associated with any particular disease or symptom complex. In this communication Crooke brought out the following additional features in respect to the pathology of the condition:

(a) A basophile adenoma was not an essential feature; and in those cases where such an adenoma was present, in none of the cells constituting the adenoma was the hyaline change found, although it was present in basophile cells throughout the remainder of the gland.

(b) Adrenal cortical hyperplasia or neoplasia was a frequent but not constant finding.

(c) In three of Crooke's twelve patients there was a neoplasm of the thymus. This complication has not been reported by other authors.

Crooke's findings in the pituitary have been amply confirmed by Eisenhardt and Thompson.[4, 5] The hyaline changes in the basophiles of the pituitary may be considered beyond reasonable doubt as the one constant pathologic finding in basophilism, and one may say that, where verification by histologic examination of the pituitary is possible, it is the sine qua non in the definitive diagnosis of Cushing's syndrome.* This statement does not imply that pituitary malfunction is necessarily the primary or initiating factor. There has been much discussion in the literature concerning the pathogenesis of this condition and the manner in which the protean physiologic aberrations and pathologic changes are mediated. These matters will be more fully considered under discussion.

Relatively few examples of Cushing's syndrome in individuals prior to puberty have been reported. Even fewer are those cases in which there has been a complete post-mortem study.

Marks, Thomas, and Warkany (1940)[7] discuss adrenocortical obesity in children in relation to twenty-three cases they collected from the literature and one case of their own. Some of the cases they described apparently would have fulfilled the requirements of Cushing's syndrome, others seemed to bear a more intimate relationship to the adrenogenital syndrome with virilism, and still others appeared to be of a mixed type or a combination of these two conditions. The authors recognized the close similarity of the findings in some cases of

*However, to practically every generalization there is always an exception. Kepler[6] quotes a case of Reforzo-Membrives & del Castillo of Buenos Aires which had been brought to his attention. The patient was typical clinically but at necropsy all the endocrine glands were grossly and microscopically normal. Sections of the pituitary showed no evidence of Crooke's changes.

adrenocortical obesity and Cushing's syndrome but apparently dismissed the possibility that in at least some of these cases they might be dealing with a preadolescent type of basophilism because pituitary adenomata occurring in children associated with Cushing's syndrome had not been described. This concept is untenable for two reasons: first, it has been repeatedly demonstrated that a basophile adenoma of the pituitary is not a constant finding in basophilism; and second, although rare, basophile pituitary adenomata in children associated with basophilism have been reported.[8-13] One of the authors, Warkany (1945),[14] however, has apparently subsequently modified his views because in the section on hyperadrenocorticism, of which he is the contributor, in Mitchell and Nelson's *Textbook of Pediatrics*, one of the subsections is entitled "Cushing's syndrome of Adrenocortical Obesity." In only one of the cases (i.e., that of Crooke and Callow[15]) cited by Marks, Thomas, and Warkany, were Crooke's changes of the pituitary described. In the protocols of most cases collected by these authors it is not possible to determine what staining techniques were employed to study the pituitary. It is possible that hyaline changes in the basophiles would have been more frequently encountered if suitable staining techniques had been employed. With routine hematoxylin and eosin preparations the characteristic hyaline changes are practically impossible to discern. However, if present, they are beautifully displayed as hyaline areas of degranulation if suitable special stains are employed, such as advocated by Crooke and Russell.[16]

Farber, Gustina, and Postoloff[17] in 1943 reviewed the cases of Cushing's syndrome in children which had been reported up to that date and added a case of their own, making a total of twenty-seven cases. In view of the close similarity of the symptom complex attributed to basophilism and that of adrenocortical obesity, it is remarkable that only one case (Crooke and Callow[15]) was common to the series of Cushing's syndrome collected by these authors and that compiled by Marks and associates[7] concerning adrenocortical obesity.

Farber and his associates did not include in their series the two cases described by Gross (1940)[18] (Cases 4 and 5) of carcinoma of the adrenal cortex with a syndrome similar to pituitary basophilism. Although both of these patients had some of the characteristics of Cushing's syndrome, neither had all the cardinal features. The pituitary in Case 4 was reported microscopically to have a cyst of the pars intermedia which compressed the pars anterior. The pituitary in Case 5 was judged microscopically to be normal. In neither case was mention made of Crooke's changes in the basophiles of the pituitary.

Albright (1943)[2] described a case of Cushing's syndrome in a girl 12 years of age. Extensive metabolic studies have been carried out on this patient. Dr. Albright[19] has informed us this patient is still living.

Heinbecker (1944)[13] reported two cases of Cushing's syndrome in children, one (Case 3, his series) in a boy 12 years of age. This appears to be a typical case of basophilism. At post-mortem examination there was atrophy of the right adrenal and hypertrophy of the left. The pituitary showed a basophile adenoma and partial hyalinization of the basophiles. He also described

atrophy of the nuclear cells of the hypothalamic and preoptic areas, particularly in the paraventricular nuclei. The author believes these changes to be of special etiological significance in respect to basophilism. His second patient (Case 5) does not appear to have a pure Cushing's syndrome but rather a mixed case of basophilism and adrenogenital syndrome, as there was also evidence of virilism. At operation a right adrenocortical tumor was removed.

Weisse (1947)[20] recorded a case of Cushing's syndrome in a female infant aged 20 months. A tumor of the left adrenal cortex was removed surgically. The infant died on the third postoperative day. A post-mortem examination was performed. The remaining adrenal was not unusual. The pituitary was apparently normal. No specific mention was made in regard to the presence or absence of Crooke's changes. This was also possibly a mixed case as evidence of virilism was present in the form of an enlarged clitoris.

Allibone, Baar, and Cant[21] reported two patients with adrenocortical obesity or Cushing's syndrome associated with adrenal cortical carcinomas. Both patients showed an extreme obesity and mild hirsutism but in neither was there masculinization or precocious growth. In one, apparently the pituitary was not examined; in the other, Crooke's changes were present in the basophiles.

Excluding the series of cases of adrenocortical obesity reported by Marks and his associates[7] the total to date of reported cases of Cushing's syndrome in children is as follows: Of the twenty-seven cases collected by Farber and associates,[17] two cases can probably be excluded, i.e., Case 2, reported by Reichmann,[22] because the patient was 36 years old at the time of death and the age of onset of symptoms was indefinite, and Case 3, reported by Teel,[23] because of insufficient clinical data. To the remaining twenty-five cases may be added the following: Gross (two), Albright (one), Heinbecker (one), Weisse (one), Allibone and associates (two), and the authors herein report an additional example of Cushing's syndrome in a child with post-mortem findings, bringing the total to thirty-three.

CASE REPORT

Clinical History.—S. G. was an 8-year-old white girl whose growth and development were normal until 4½ years of age (Fig. 1). Shortly after this time she began "to put on weight" and seemed "fat in the face." Her family physician judged her to be overweight but otherwise normal. During the ensuing three and one-half years the abdomen became protuberant and excessive weight gain continued. Diet restriction and thyroid extract were employed without success.

One year after the onset of the obesity, stunting of stature became increasingly evident, and in the three years prior to hospitalization there was no appreciable gain in height.

At approximately 7 years of age her mother noted the appearance of pubic hair. There were occasional episodes of back pain and abdominal discomfort. The child also complained of intermittent headaches of moderate severity. No polyphagia, polydipsia or polyuria were noted. She had never menstruated and had the normal, high-pitched voice of a child.

Concomitant with the development of the unusual changes in body contour, her general health was considered to be satisfactory. Progress at school was normal but she was unable to take an active part in playground games with other children because of some exertional dyspnea.

Fig. 1.—Patient S. G. to the right, at age of 4½ years, with her younger brother.

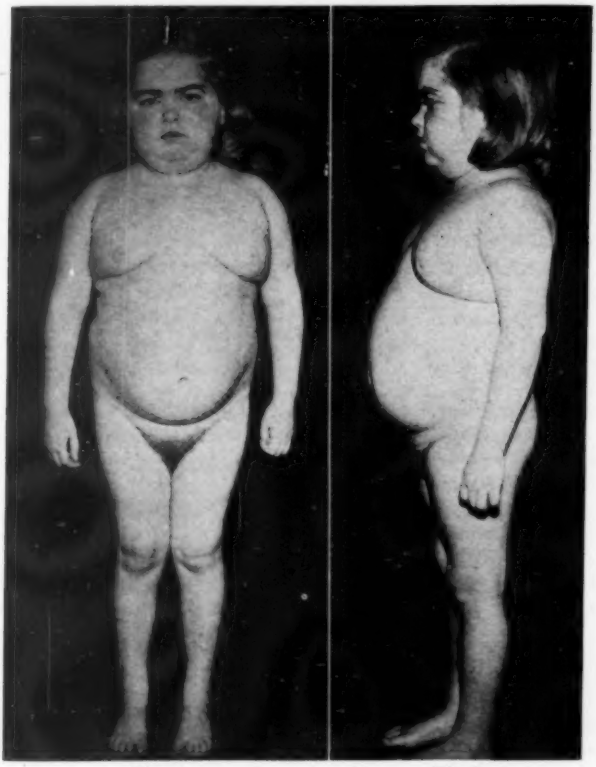

Fig. 2. Fig. 3.

Figs. 2 and 3.—S. G. at time of admission, 8 years of age.

Family History.—The immediate family history was not significant. A distant female cousin of our patient died at 10 years of age with primary atrophy of the adrenal glands.* The maternal grandmother of this cousin and the maternal grandfather of our patient were brother and sister. Although this is probably coincidental, it seems unusual that even distant cousins should suffer from two rare maladies in which the adrenal cortex is involved.

Physical Examination.—This girl was short, 44½ inches (111.25 cm.) and showed the characteristic "buffalo" obesity involving the face and trunk and sparing the extremities (see Figs. 2 and 3). Her weight was 65 pounds (29.5 kilos). Her face was broad and florid with full cheeks and prominent double chin. The chest and shoulders were broad and thick with pendant, widely separated, flabby breasts in which no glandular tissue was felt. The abdomen was protuberant. Over the flanks and upper thighs there were purple striae. There was a prominent fat pad at the base of the neck, the shoulders were rounded, and the spine had lost the normal dorsal and lumbar curves. The extremities were little involved in the obesity and seemed slender in relation to the trunk. On the face, extremities, and back was present an excessive growth of fine, soft, fair hair. Crisp dark hair was present in the axillae and over the pubes, the latter showing the female distribution. Mild acne was noted on the face. The eyes, ears, nose, and throat were negative. The neck was short and thick. There were no enlarged glands. The thyroid was not palpable. The chest was symmetrical with good expansion. The lungs were clear to percussion and auscultation. The heart was not enlarged, sounds clear, normal rate, and rhythm regular. The blood pressure was 148/100. No organs or tumor masses could be palpated through the obese abdominal wall. Although there was an abundant growth of pubic hair, the external genitalia were not unusual. The clitoris was not enlarged. A vaginal examination was not done. The reflexes were physiologic.

Laboratory Investigations.—Urine: Urine was acid; albumin, 0; sugar, trace, and repeated samples were negative; microscopic examination, sediment showed occasional white blood cells.

Blood: Hemoglobin was 16.6 Gm.; red blood cells, 5,100,000; hematocrit, 50 per cent; and white blood cells, 17,600.

Blood chemistry: Serum calcium was 5.12 meq. per liter (10.3 mg. per cent). Inorganic serum phosphorus, 1.9 meq. per liter (3.4 mg. per cent). Serum alkaline phosphatase, 20.3 King Armstrong units. Nonprotein nitrogen, 34.8 mg. per cent. Fasting blood sugar, 87.0 mg. per cent. Serum chlorides, 103.1 meq. per liter (598 mg. per cent NaCl). Serum sodium, 140.8 meq. per liter (324 mg. per cent).

Glucose tolerance test using 100 Gm. of glucose: urine, negative each time; blood, at fasting, 79 mg. per cent, at thirty minutes, 121 mg. per cent, at sixty minutes, 154 mg. per cent, at one hundred twenty minutes, 120 mg. per cent, at one hundred eighty minutes, 115 mg. per cent.

Total neutral 17-ketosteroids excretion, 6.2 mg. per twenty-four hours.

Calcium balance test, negative balance with hypercalcinuria: calcium intake, 1 Gm. per 24 hours; calcium in urine, 1.3 Gm. per twenty-four hours; calcium in stool, 0.12 Gm. per twenty-four hours.

Nitrogen balance test, positive balance: nitrogen intake, 37.9 Gm. per seventy-two hours; nitrogen excreted in stool in seventy-two hours, 7.16 Gm. Nitrogen excreted in urine in seventy-two hours, 22.5 Gm.

Basal metabolism rate, -12. Corrected for normal weight for height, +3.

Postoperative determinations: serum chloride, 109.2 meq. per liter (634.4 mg. per cent NaCl); serum sodium, 134.8 meq. per liter (310 mg. per 100 c.c.); nonprotein nitrogen, 35.4 mg. per cent.

X-Ray Examination.—All the bones visualized showed a generalized osteoporosis. The dorsal and lumbar spine presented an unusual amount of osteoporosis and a lack of the normal dorsal and lumbar curves. Some of the vertebrae, particularly the twelfth dorsal and the first lumbar, showed evidence of compression. The intervertebral spacings were increased in width (Fig. 4).

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*We are indebted to Dr. R. E. Miller of the Department of Pathology and Bacteriology, Dartmouth Medical School, for furnishing us with details of the post-mortem findings on this girl.

Progress.—There was no essential change in this child's condition while she was under investigation in the hospital. A clinical diagnosis of Cushing's syndrome was made, probably associated with adrenal hyperplasia or tumor. As it was the consensus of many consultants that untreated her prognosis was poor, it was decided to explore her and remove one adrenal if no tumor was found.

Fig. 4.—Lateral roentgenogram of dorsal and lumbar spine, showing osteoporosis, collapse, and wedging of the vertebral bodies, particularly T12 and L1.

Operation and Postoperative Course.—On the night preceding operation, she received 15 c.c. of Adrenal Cortical Extract* subcutaneously and immediately prior to operation, 15 c.c. intravenously. Codeine and hyoscine were used for preoperation sedation. Under ether anesthetic an exploratory operation was performed. No adrenal tumor was present. The left adrenal gland was removed, together with several small yellow to brown-red nodules from the periadrenal fat. This gland was similar in all respects to the right. Both will be described with the post-mortem findings. The child withstood the operation well and seemed bright and comfortable after consciousness had been regained. The postoperative blood pressure was 120/110, the pulse, 120. During the next ten hours the pulse became rapid and irregular. Despite the intravenous administration of a total of 43 c.c. of adrenal cortical extract, the blood pressure fell steadily to 106/86. Quite suddenly, twenty-two hours postoperatively, her

*Connaught Medical Research Laboratory Adrenal Cortical Extract, biologically standardized to contain 30 units per cubic centimeter, was employed.

pulse and blood pressure became unobtainable and remained so for one hour. The blood pressure then returned to average about 80/65. Following this she became anuric and her serum chlorides (109.2 meq. per liter) began to rise. Serum sodium (134.8 meq. per liter) was slightly below normal and the nonprotein nitrogen was within normal limits. She also complained of pain in the left chest posteriorly and the possibility of a pulmonary embolus or massive collapse was considered. However, this was not confirmed by x-ray.

During the second postoperative day the blood pressure remained about 65/50 although the child continued to seem bright and adjusted her own covers. Despite continued administration of adrenal cortical extract (80 c.c.) the blood pressure again became unobtainable, her temperature rose to 104° F., coma ensued, and she died forty hours postoperatively.

AUTOPSY

Gross.—Externally, in addition to the obesity, the body showed the peculiar stigmata of Cushing's syndrome described in the clinical section. The abdominal fat measured 3 cm. in thickness and there were large masses of adipose tissue in the omentum and paravertebral gutters. Fat necrosis was noted in the depths of the recent surgical incision in the left flank. The thymus was atrophied. The heart (weight, 163 grams) showed a moderate degree of left ventricular hypertrophy. The lungs displayed a few small areas of superficial collapse.

Fig. 5.—Left and right adrenal, respectively. Note the extreme nodularity of the cortex.

The alimentary tract was normal. The liver (weight, 886 grams) was slightly enlarged and fatty. The pancreas (weight, 58 grams) was normal in size. Typical patchy, chalky-white areas of fat necrosis were present both about the periphery and in the substance of the gland. This was most marked in the tail, the left periadrenal fat, and around the upper pole of the left kidney which areas were adjacent to operative site. The spleen was normal. The kidneys were normal except for fat necrosis about the upper pole of left kidney. The uterus and tubes were normal preadolescent. The ovaries were slightly enlarged (length, 3 cm.). Numerous small follicles were visible under the peritoneal surface. Cancellous bone removed from the lumbar vertebra was softer than usual but there was no gross abnormality of the bony trabeculae. The brain was normal. The pituitary (weight, 338 milligrams) appeared normal in size and shape. The left adrenal (weight, 4.7 grams) removed at operation showed the same extraordinary appearance as the right (weight, 5.3 grams). They were both approximately normal

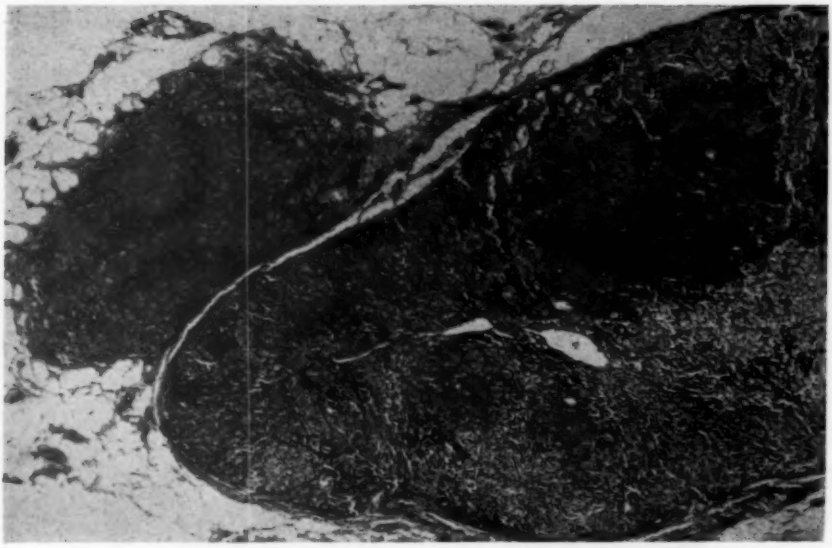

Fig. 6.—Photomicrograph, left adrenal, low power, hematoxylin and eosin stain. A large nodule of hyperplastic tissue has "invaded" the periadrenal fat. Another nodule of hyperplastic cortical tissue is present within the adrenal cortex.

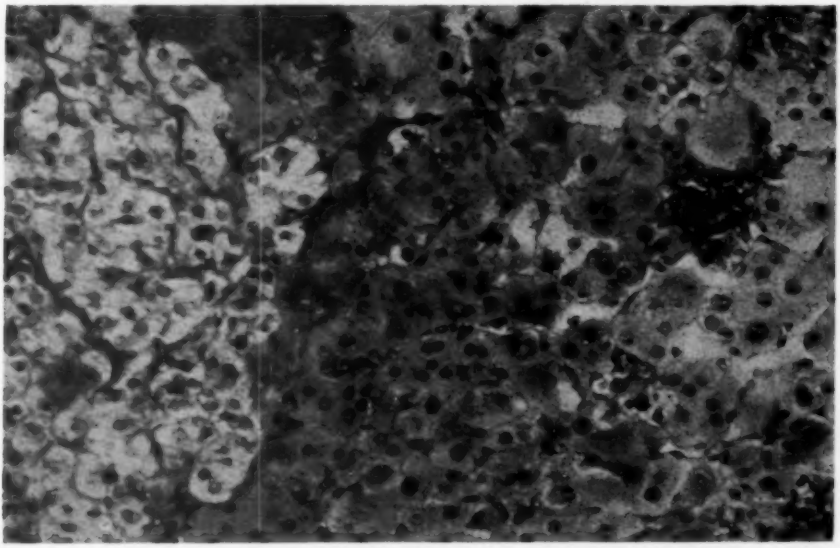

Fig. 7.—Photomicrograph, left adrenal, medium power, hematoxylin and eosin stain. Hyperplastic cortical cells. The cytoplasm of the cells to the left is vacuolated due to lipid content. A focus of lymphocytic infiltration is shown.

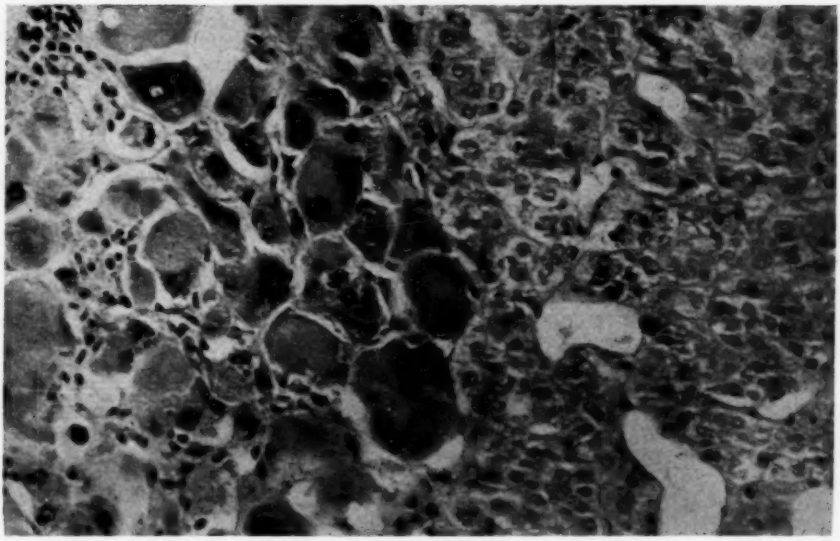

Fig. 8.—Photomicrograph, right adrenal, medium power, hematoxylin and eosin stain. Note the hyperplastic giant cortical cells. No mitotic figures were seen.

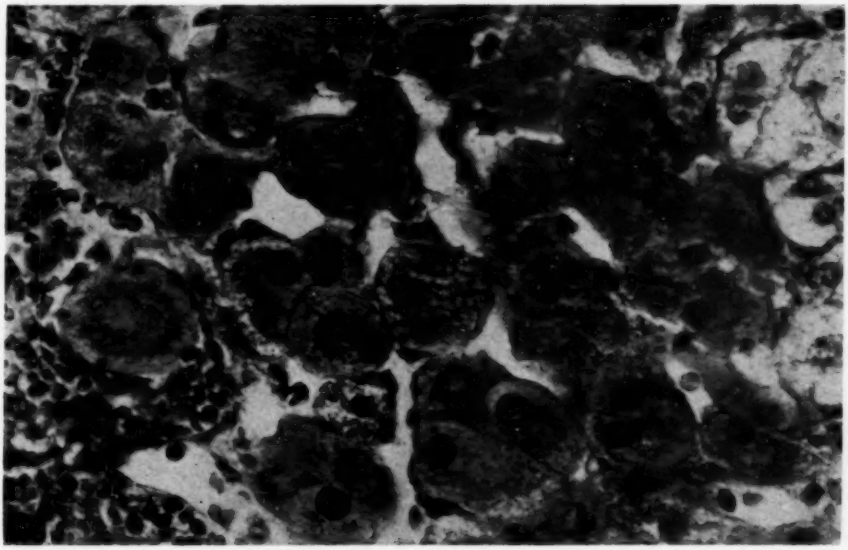

Fig. 9.—Photomicrograph, right adrenal, medium power, hematoxylin and eosin stain. Giant cortical cells. In some of the cells the lipochrome pigment is present in a curious ring pattern.

in size and shape but the cortical surfaces were studded with numerous smooth, round, globular excrescences varying in size from 1 to 5 mm. (Fig. 5). These nodules shaded in color from dull yellow to dark brown-red, imparting to the glands a peculiar irregular variegated appearance. The cut surface of the adrenals revealed that the nodules were solid and appeared circumscribed. They obviously originated in the cortical tissue and had displaced and replaced the major portion of the normal cortex, the remnants of which could be seen between the nodules. At operation the surgeon removed from the left periadrenal fat numerous (fifteen to twenty) small hemorrhagic nodules 1 to 2 mm. in diameter. Microscopic sections revealed that most of these were small localized areas of hemorrhage but three contained tiny masses of hyperplastic adrenocortical tissue. At the post-mortem examination a careful search was made for more of these nodules in the neighborhood of the operative site and around the right adrenal, but none were found.

Microscopic Examination.—

Adrenals: In all sections studied there were numerous adenomatous nodules of hyperplastic adrenal cortical tissue, some of which had expanded through the capsule of the gland and had invaded the surrounding fat (Fig. 6). Between the nodules there were areas of normal appearing adrenal cortex which, however, represented only a small proportion of the total cortical tissue. The cortical tissue comprising the hyperplastic adenomata presented a bizarre and variegated picture. The cortical cells varied tremendously in size, shape, and staining qualities and most were larger than the normal. In some, the cytoplasm was abundant and eosinophilic; in others, it was replaced by large amounts of lipid (Fig. 7). Many of these abnormal cortical cells were giant forms with irregular, distorted, dark-staining nuclei (Fig. 8). In many of the giant cells there were cytoplasmic deposits of yellow-brown lipochrome pigment which occasionally was arranged in a peculiar ring pattern (Fig. 9). Mitotic figures were not encountered in spite of the hyperplastic appearance of these cortical adenomata. Scattered throughout the adenomata were focal accumulations of lymphocytes. In spite of the unusual variation in the size, shape, and staining qualities of the hyperplastic adrenal cells, and extension beyond the capsule of the adrenal, they did not appear to have undergone malignant change. The numerous small nodules removed by the surgeon from the left periadrenal fat were for the most part composed of recent hemorrhage. A few contained nodules of the peculiar hyperplastic adrenal cortical tissue identical with that in the adrenals proper. These were considered to be adrenal rests which had undergone the same hyperplastic change as had occurred in both adrenal cortices rather than metastatic deposits as a result of malignant change in the adrenal cortical tissue. Sections of the adrenal were stained by the ponceau-fuchsin method recommended by Broster and associates[24] and none of the fuchsinophilic material was present.

Pituitary: The gland was sectioned serially and no adenoma was found. Typical Crooke's changes were present in the majority of the basophiles of the anterior lobe (Fig. 10). The degree of the loss of granularity or hyalinization varied from cell to cell but completely normal appearing basophile cells could be found only in the region adjacent to the pars intermedia. The pars posterior and pars intermedia were normal.

Brain: In view of Heinbecker's[13] work, particular attention was paid to the hyothalamic area of the brain. Numerous blocks were taken through this region, including the paraventricular and supraoptic nuclei. No significant lesions were encountered. The pineal gland was normal.

Pancreas: Scattered foci of typical fat necrosis were present in the pancreas and peripancreatic fat. Islet tissue was normal in amount. Differential stain showed no abnormal variation in the granulations of either the α or β cells.

Liver: There was excessive accumulation of fat in the liver cells with a predilection for the midzonal area of the liver lobule.

Kidneys: No abnormal changes were discernible in spite of the terminal anuria.

Bone: Sections of the vertebrae showed the bone trabeculae to be more widely spaced and more delicate than normal but otherwise not unusual. The marrow was normal.

Breast: There was proliferation of the ducts but no evidence of acinar proliferation (Fig. 11).

The heart, lungs, spleen, thymus, thyroid, uterus, tubes, and ovaries were within normal limits. Unfortunately, the parathyroids were not obtained.

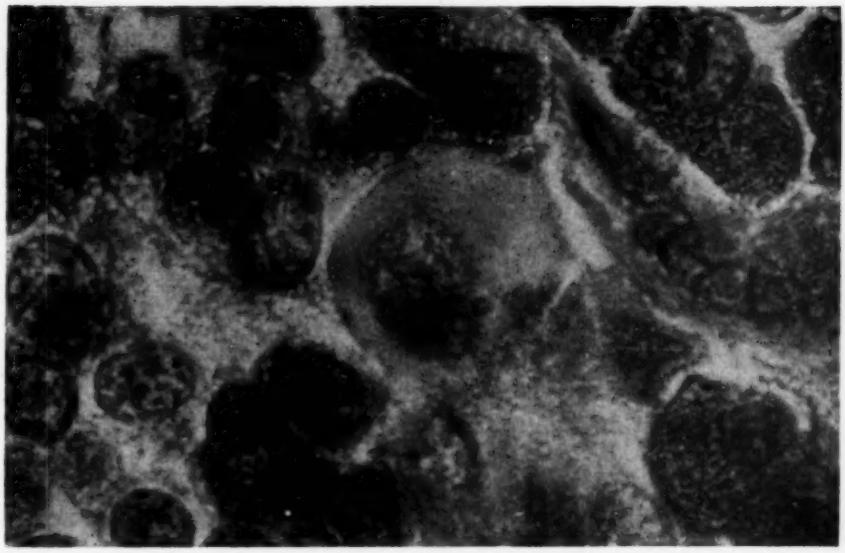

Fig. 10.—Pituitary gland, oil immersion, Mann's stain. In the center is a basophile with typical Crooke's hyaline change. A few basophilic granules are present at one side of the nucleus and a clump at the periphery of the cell.

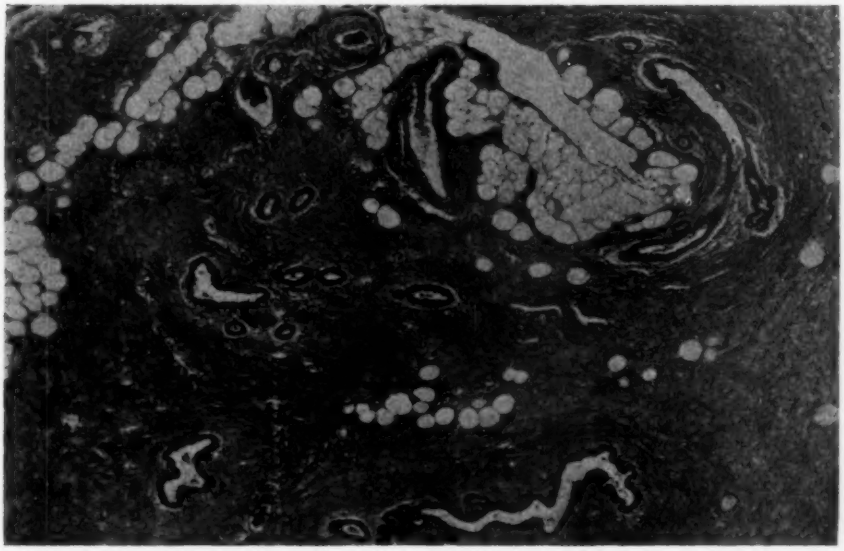

Fig. 11.—Breast, low power, hematoxylin and eosin stain. There is duct proliferation but no development of acinar tissue.

TABLE I. CLINICAL AND POSTMORTEM FINDINGS IN EIGHTEEN

NO. AUTHOR OF CASE	YEAR OF PUBLICATION	SEX	DURATION OF SYMPTOMS (YEARS)	AGE AT DEATH (YEARS)	CLINICAL: TYPICAL OBESITY	PLETHORA	LINEA ATROPHICA	HIRSUTISM	VIRILISM	BLOOD PRESSURE	OSTEOPOROSIS	MUSCULAR WEAKNESS	DECREASED SUGAR TOLERANCE	POLYCYTHEMIA	URINARY EXCRETION OF HORMONES
1. Bauer and Wassing[3]	1913	M	7/12	16	+	+	+	+	-	180/-	+				
2. Leyton et al.[25]	1931	M	1/12	11	+	+	-	+	-	125/85	-		+	-	
3. Bishop and Close[9]	1932	F	11	22	+	+		+	-	250/180	+		+		
4. Jamin*[26]	1934	M	?	19	+		+	+	-	160/100	+		-	+	
5. Wright and Courville[10]	1935	M	1½	11	+	+	+	+	-	200/150	+	+	+	+	
6. Freyberg et al.[11]	1936	M	7	19	+	+	+	-	-	175/155	+	+	+	-	
7. Rasmussen†[27]	1936	M	?	13	+	+	+	+	-	+	+		+	-	
8. Lawrence[28]	1937	M	1	14	+	+	+	+	-	145/90	+	+	+	-	Prolan normal
9. Shoykhet and Palchewsky[12]	1937	M	3	17	+	+	+	+	-	178/148	+		-	+	
10. Crooke and Callow (Case 2)[17]	1939	F	1/12	6	+	+	+	+	+	150/120	-	+	-	-	17 ketosteroids increased
11. Gross (Case 4)[18]	1940	F	3/12	10	-	+		+	-	160/120		+	+	-	
12. Gross (Case 5)[18]	1940	F	3/12	3	+	+			-	190/160		·	+	±	
13. Farber et al.[17]	1943	M	1	15	+	+	+	+	+	190/156	+	+	+	+	
14. Heinbecker (Case 3)[13]	1944	M	2	12	+	+	+	+	-	150/126	+	+			
15. Weisse[20]	1947	F	1	18 1/12	+	+	+	+	+	170/130		+	-	-	Normal
16. Allibone, Baar, and Cant (Case 19)[21]	1947	F	4/12	9/12	+			-	-		-		-		
17. Allibone, Baar and Cant (Case 20)[21]	1947	F	1	18 1/12	+	+		+	-		-		-		
18. Present case	1948	F	3	8	+	+	+	+	-	146/100	+	-	+	±	17 ketosteroids increased

*Post-mortem findings not published; pituitary examined by Eisenhardt.[6]
†Unable to find published data of complete post-mortem examination.[27] Case cited by Farber et al.[17]

EIGHTEEN CASES OF CUSHING'S SYNDROME IN CHILDREN

	POST MORTEM								
ADRENAL CHANGES	PITUITARY TUMOR	CROOKE'S CHANGES	HYPOTHALAMUS	INTERNAL GENITALIA	THYROID	PARATHYROID	THYMUS	PANCREAS	KIDNEYS
	Basophile adenoma			Large testicles	Enlarged	Normal	Atrophy		Nephritis
Enlarged: total wt., 20.6 Gm.	None	+		Normal	Large		Carcinoma	Normal	Normal
Normal	Basophile adenoma	+		Normal	Normal				"Scarring"
	None	±							
Normal	Basophile adenoma	+			Normal	Normal		Acute pan'itis	
Hypoplasia	Basophile adenoma	+		Atrophy of gonads	Normal	Fatty atrophy	Large 75 Gm.	Islets increased	Nephritis
Carcinoma left adrenal	None	+							
Hypertrophy: total wt., 15 Gm.	Adenoma, ant. lobe, type?			Infantile	Normal		Atrophy	Fat necrosis	
"Well developed"	Basophile adenoma			Atrophy of gonads		Atrophy	Atrophy		Nephritis
Carcinoma of cortex, left	None	+							
Carcinoma of cortex, right	Cyst pars intermedia			Infantile			Normal		Normal
Adenocarcinoma left	None								
Carcinoma of cortex, right	None	+		Interstitial tissue increased	Normal				Nephritis ?
Right hypertrophy Left atrophy	Basophile adenoma	+	+	Suppressed spermatogenesis		Fat involution	Atrophy	Islets increased	
Tumor left adrenal	None				Advanced for age		Atrophy	Islets increased	Normal
Right carcinoma Left small	None								
Left carcinoma Right hypoplasia	None	+					Atrophy		
Bilateral hyperplasia	None	+	-	Enlarged ovaries	Normal		Atrophy	Fat necrosis	Normal

CASE SUMMARY

A typical clinical case of Cushing's syndrome in a girl 8 years of age, who died approximately two days after the removal of one adrenal, is described. In addition to the somatic stigmata of this syndrome the main pathologic changes were: Crooke's changes in the pituitary gland, bilateral nodular hyperplasia of the adrenal cortex, fatty liver, and osteoporosis. An operative complication was pancreatic fat necrosis. The presence of numerous, small, nodular hemorrhages occurring in close proximity but not actually in the operative site was sufficiently unusual that the surgeon removed some of them for section. It is probable that these were an index of the extreme lability of the tissue to injury and hence may account for the development of the pancreatic fat necrosis.

PATHOLOGY OF CUSHING'S SYNDROME IN CHILDREN

Of the thirty-three cases of Cushing's syndrome or basophilism reported in children, eighteen have come to post-mortem examination. In Table I the significant clinical and pathologic features of the eighteen autopsied cases have been summarized. It is seen that the clinical pattern in children diverges in no fundamental way from that encountered in adults. Likewise, the pathologic changes show the same general trends and variations as found in adults.

In an attempt to assess the pathogenesis of this obviously metabolic disease, aberrations in the physiology of the adrenals and/or the pituitary are usually postulated. From Table I the following facts emerge in respect to the pathologic changes found in basophilism.

1. Crooke's hyaline changes in the basophiles of the pituitary were present in all cases in which the pituitary was examined and these lesions were specifically mentioned. Present in eleven cases, not mentioned in seven.

2. Pituitary adenomata were frequent but not constant: present in a total of seven cases; basophilic in type in six; and in one case not specified.

3. Presumptive histologic evidence of adrenal overactivity was present in thirteen cases of the eighteen. Carcinoma of adrenal cortex in eight, hyperplasia in five. In two the adrenals were stated to be normal and in two the condition of the adrenals was not mentioned.

In addition, the following are frequently associated findings which may or may not be significant:

1. Occasionally there is evidence of stimulation of the gonads but more often the changes are retrogressive.

2. The nerve cell changes present in the hypothalamic region in Heinbecker's case were not present in ours. The presence or absence of lesions in this area were not mentioned in any other report.

3. Increase in the number of islets of the pancreas was noted in three cases. Pancreatic fat necrosis was present in three operative cases. Albright[19] has drawn our attention to the prevalence of this complication following operation in cases of basophilism.

4. Nephritis is common. Of the eight cases in which the condition of the kidneys was mentioned, it was present in four.

DISCUSSION

Cushing was the first to focus attention on the syndrome which now bears his name. He was impressed with the presence of basophile tumors in the pituitary gland of the patients he studied, and thought that they were the cause of the condition. Later work failed to confirm the presence of a pituitary tumor in many undoubted cases of this disease and attention became directed to the adrenal cortex because of the frequency of associated abnormalities of this gland. Crooke's work, in which he demonstrated hyaline changes in the cytoplasm of the basophile cells, again emphasized the importance of the pituitary in any consideration of this syndrome.

In reviewing the changes which are encountered in this condition most of the more important ones seem to be best explained on the basis of adrenal cortical overactivity. The chief exponents of this theory are Albright,[2] Kepler,[6] and Soffer.[29, 30] However, it is possible that the pituitary, by means of the adrenocorticotropic hormone, initiates the changes, or it may be, as Kepler suggests, that the pituitary changes are secondary to adrenal-cortical overactivity.

Three major effects have been ascribed to the adrenal cortex: (1) regulation of salt metabolism; (2) regulation of carbohydrate metabolism; (3) interaction with the gonads in the sexual development of the individual, which action is probably associated with changes in nitrogen metabolism.

Hyperfunction of the adrenal cortex may be associated with diffuse hyperplasia, benign adenoma, or a neoplasm of the adrenal cortex. Clinically there are two distinct syndromes which may occur as a result of hyperadrenocorticism: (a) the adrenogenital syndrome and (b) Cushing's syndrome.

The adrenogenital syndrome is the result of an overproduction of a masculinizing hormone(s) possibly closely related to the N hormone(s) of Albright. There is apparently little upset in general metabolism with the exception of excessive tissue development (i.e., nitrogen retention). In the male individual this produces premature sexual development and in the female it may produce pseudohermaphrodism if the androgenic principle is overactive during intrauterine life, and pseudoprecosity and masculinization if the stimulation occurs subsequent to birth.

In a pure Cushing's syndrome there is no evidence of true masculinization such as alteration of the voice or enlargement of the clitoris in the female; however, there are many other changes such as obesity, osteoporosis, and disturbed carbohydrate metabolism, which are not encountered in a pure adrenogenital syndrome. It is obvious that in some cases the overactivity of the adrenal cortex is associated with a syndrome which is a mixture of the adrenogenital complex and Cushing's syndrome. Many of the cases collected by Marks, Thomas, and Warkany[7] fall into this group.

In the Cushing's syndrome which especially concerns us here the major findings are related to an abnormal metabolic picture. The most exhaustive attempt to explain the clinical and chemical change encountered in this disease is that of Albright.[2] He has put forth the theory that hyperadrenocorticism with respect to the "S" or sugar hormone is the cause of this disease. He considers

the action of this hormone to be *antianabolic* rather than *catabolic* in nature. Hence the basic condition, he argues, is not an increased destruction of, but rather a failure to produce, tissue. The thin skin, lack of muscle, even the osteoporosis, are thought to be due to a deficient laying down of protein.

The "S" hormone is known to favor the conversion of protein to amino acids. Some of these may become available for conversion to carbohydrate. This, together with the fact that the "S" hormone interferes with the oxidation of carbohydrate, accounts for the low carbohydrate tolerance in these cases.

The hirsutism and moderately elevated 17-ketosteroid excretion in the urine he explains on the basis of a compensatory increase in the "N" (nitrogen) hormone(s) of the adrenal. This hormone(s) causes increased tissue formation and would tend to restore the normal physiologic balance.

The beneficial effects of testosterone in these cases he explains by the fact that it produces the same effects as the "N" hormone in building tissue. Indeed, the two hormones may be closely related chemical compounds.

Albright has postulated hyperadrenocorticism to explain the findings in Cushing's syndrome. He has had to include two hormones producing opposite effects to account for the major findings. Up to the present at least twenty-five active principles have been isolated from the adrenal cortex.[29] Undoubtedly many more will be discovered. It seems likely to the authors that while Albright's statement of the case gives the broad outline of the picture, the detailed interpretation will depend on the correlation of the activity of all these various substances. An illustration of this is provided by the different effects produced by whole adrenal cortical extract and desoxycorticosterone. Hypertension and increased salt retention can be brought about by excessive administration of desoxycorticosterone but not by administration of the whole extract.

It was seem, therefore, that in whole adrenal cortical extract there is a balancing effect between the various substances, one upon the other, while in Cushing's syndrome there is some alteration in the proportion of these components. The extent of these alterations may vary from one patient to another. Thus, in the cases which have been reviewed there was considerable variation in the extent of clinical findings. For example, in come patients, virilism, as indicated by hirsutism and enlarged genitalia, was marked, though in the majority hirsutism without genital enlargement was the rule. In some, osteoporosis was marked; in others, it was less prominent. Some had a definite diabetes; others had only mild signs of carbohydrate intolerance. The same may be said for any of the other features of the disease. These variations tend to support the theory that there are a number of substances that may be abnormally active.

On the other hand, the fact that such a uniform clinical picture is presented in this disease, argues for some fundamentally similar change in all cases. The possibility arises that this fundamental change may be due to some abnormal substance elaborated by the adrenal, but so far there is no proof for this hypothesis. Since many of the findings can be explained by known effects of adrenal extracts, it seems more likely that some derangement of the normal mechanism is at fault. At present we have insufficient knowledge to draw a complete picture of what these changes are.

While the preceding discussion has assumed that the adrenal is the seat of the disorder, a view which is ably defended by Kepler,[6] there is still the possibility that the pituitary is the initiating factor. Kepler argues that the almost universal finding of Crooke's changes in the basophile cells of the pituitary is a secondary, rather than a primary effect. In support of this he points out that removal of an adrenal tumor such as a carcinoma has caused a remission in the symptoms of the disease. On the other hand the absence of demonstrable changes in the adrenal in some cases has made it difficult to incriminate this organ as the cause of the disease in every case.

A recent article by Conn, Louis, and Wheeler[31] throws some additional light on the interrelationships between the pituitary, adrenal cortex, and the metabolism of carbohydrates and protein. These authors produced a diabetic state in all of three normal subjects by daily intramuscular injections of purified pituitary adrenocorticotropic hormone. In addition, two of the subjects developed a negative nitrogen balance during the period of hormone administration, despite an adequate protein intake. These findings would appear to favor Albright's contention that the metabolic disturbances of Cushing's syndrome are mediated through the adrenal cortex. However, it cannot be gainsaid that in some cases, particularly when there is bilateral hyperplasia of the adrenal cortices, the initiating stimulus may arise in the pituitary.

That there is a marked interdependence of the adrenal and pituitary glands upon each other is well known, and the apparent beneficial effect of irradiating the pituitary in Jamin's[26] case may be explained on this basis.

Heinbecker[13] has described changes in the hypothalamic nuclei and thinks there may be a relationship between these findings and the basophile hyaline changes. He suggests that these hypothalamic changes may bear a causal relationship to the disease. No other authors have described these changes and none was found in our case.

The treatment of these cases presents many problems. Since reports of cures following removal of an adrenal tumor have been published, it was decided to explore our patient with the hope of removing an adrenal tumor if one were present. At operation an obviously abnormal adrenal was found on the left side. Palpation of the right adrenal at this time indicated to the surgeon a gland of apparently normal size. Consequently, the abnormal left gland was removed. It was felt that a similar condition might be present on the right but by the removal of one abnormal adrenal it was hoped that some measure of improvement might be gained. Had the patient survived, testosterone therapy as suggested by Albright was contemplated. The reason for this patient's death is not clear, since her sudden fall in blood pressure did not occur until twenty-four hours after her operation. Whether the acute pancreatic necrosis was the cause of the acute circulatory collapse is a matter of conjecture. It is generally known that these patients are a poor operative risk and that death often occurs for no apparent reason.

As the life expectancy of untreated patients is not great, and because of their increasing physical deformity, radical measures of treatment may be justified. However, the treatment of these patients should be undertaken accord-

ing to a set programme. The reader is referred to Soffer's article[30] for details of this procedure.

SUMMARY

The literature of Cushing's syndrome or basophilism in children has been reviewed with particular reference to the seventeen cases which have come to post-mortem examination.

An additional case in an 8-year-old white girl is reported, together with the clinical and post-mortem findings.

The majority of the clinical and experimental evidence at present available suggests that the physiologic and pathologic changes in this syndrome are due to an imbalance of the hormones of the adrenal cortex. However, the role of the pituitary as a causative or initiating factor cannot be entirely discounted, in view of the fact that the hyaline change in the basophiles of this gland is the most constant pathologic change in this disease.

Further knowledge must be gained before this condition is thoroughly understood and before adequate treatment can be given.

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OBSERVATIONS ON THE USE OF PROCAINE-PENICILLIN

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IN ORDER to obtain prolonged high serum penicillin titers following a single injection, a number of different penicillin preparations have been developed. All such preparations must be shown to be nontoxic and must be capable of maintaining therapeutic serum penicillin titers for a prolonged period following a single injection. Procaine-penicillin is one of the newer preparations, and the purpose of this report is to record our findings in its clinical use.

METHOD OF STUDY

The procaine-penicillin used is marketed as Duracillin and was kindly furnished by Eli Lilly and Company.* It is a crystalline salt of procaine penicillin-G, suspended in sesame oil.[1] It remains in a fluid state at room temperature and is quite stable. Each cubic centimeter contains 300,000 units of penicillin and 124.5 mg. of procaine base. A dry syringe and a 20-gauge needle are used for intramuscular injection.

Serial serum penicillin titers following a single injection of Duracillin were determined in a group of thirteen well children. The subjects were of varying weights and ages. No attempt was made to calculate the penicillin dosage by an exact number of units per unit of body weight. Instead, an arbitrary amount of 150,000 units was given to infants under 11 kg. body weight, and 300,000 units were given to children over this weight. Blood was drawn at varying intervals following a single injection of Duracillin and serum penicillin titers were determined by a tube dilution method using FDA *Staphylococcus aureus* 209P as the test organism. In most instances penicillin titers were not carried above 1.0 or 2.0 units per c.c., as this was not felt necessary for the purposes of this study.

RESULTS

Penicillin titers obtained in ten normal children following one injection of Duracillin are outlined in Table I. Twelve hours after injection, the penicillin titers were greater than 1.0 unit per cubic centimeter in seven cases. In two instances the titer was 0.2 unit per cubic centimeter, and in only one was the titer 0.1 unit per cubic centimeter. In no case was a level of less than 0.1 unit per cubic centimeter found twelve hours after injection. Twenty-four hours after injection titers were determined in eight of these patients and in seven instances varied from 0.1 to 1.0 unit per cubic centimeter. In only one patient was a titer of less than 0.1 unit per cubic centimeter found. A few variations are seen in titers of Patients 4, 8, and 9, where a low titer is followed by a higher

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one. These could be due to mechanical factors influencing absorption. In two of the three instances, a borderline reading in the next lower tube produced this apparent variation.

TABLE I. SERUM PENICILLIN TITER IN UNITS PER CUBIC CENTIMETER AFTER ONE DURACILLIN INJECTION IN NORMAL CHILDREN

PATIENT	WEIGHT (KG.)	PENICILLIN (UNITS)	HOURS AFTER INJECTION								
			1	2	4	8	12	16	18	20	24
1	4.7	150,000	—	—	>2.0	—	>2.0	—	—	1.0	1.0
2	5.5	150,000	—	>1.0	—	—	>1.0	0.5	—	0.2	0.1
3	5.9	150,000	—	>1.0	>1.0	>1.0	>1.0	—	1.0	—	—
4	8.0	150,000	—	—	>1.0	—	>1.0	0.5	—	1.0	0.2
5	23.0	300,000	—	>1.0	>1.0	>1.0	>1.0	—	0.5	—	—
6	26.0	300,000	—	—	>1.0	—	>1.0	>1.0	—	0.5	0.2
7	34.5	300,000	—	—	0.5	—	0.2	0.2	—	0.1	0.1
8	35.0	300,000	—	—	0.5	—	0.2	0.5	—	0.5	0.2
9	38.0	300,000	—	—	>1.0	—	>1.0	>1.0	—	0.2	1.0
10	42.0	300,000	—	—	0.5	—	0.1	0.1	—	<0.1	<0.1

Table II records serum penicillin titers in three patients at more frequent intervals following one injection of Duracillin. Very rapid penicillin absorption is manifest with titers of 1.0, 2.0, and 6.5 units per cubic centimeter being found one-half hour after injection. The peak level was found one hour after injection in two patients and one-half hour after injection in the third. Eight hours after injection the titers ranged from 0.5 to 1.0 unit per cubic centimeter. After twenty-four hours two patients had less than 0.1 unit per cubic centimeter, although one had 1.0 unit per cubic centimeter.

TABLE II. SERUM PENICILLIN TITERS AT INTERVALS AFTER INJECTION OF DURACILLIN IN THREE CHILDREN

PATIENT	WEIGHT (KG.)	PENICILLIN (UNITS)	HOURS AFTER INJECTION						
			½	1	2	4	8	12	24
1	6.6	150,000	2.0	4.0	2.0	1.0	0.5		0.1
2	13.5	150,000	1.0	>1.0	1.0	0.5	0.5	0.5	0.1
3	13.5	300,000	6.5	5.0	4.0	4.0	1.0		1.0

In both Tables I and II there is no exact correlation between serum penicillin titers and the amount of penicillin administered. In general, however, higher titers were found in patients who received relatively larger amounts in proportion to body weight.

THERAPEUTIC RESULTS

Forty-one sick children were treated exclusively with Duracillin. They are classified as follows: those with otitis media and nasopharyngitis, 6; bronchiolitis, 5; bronchopneumonia, 5; laryngotracheobronchitis, 6; cellulitis and adenitis, 2; acute tonsillitis, 4; conjunctivitis, 1; lobar pneumonia, 5; osteochondritis, 1; congenital syphilis, 1; subacute bacterial endocarditis, 1; upper respiratory infection, 4. Children who were moderately or severely ill were given penicillin in the above outlined amounts every twelve hours until clinical improvement was noted, after which the injections were given at twenty-four hour intervals.

In Table III are summarized penicillin titers found in this group of sick children treated with Duracillin. These titers varied from 0.2 to 4.0 units per cubic centimeter twelve hours after injection. Twenty-four hours after injection the levels varied from less than 0.1 to 1.0 per cubic centimeter. Most of the twenty-four-hour levels ranged from 0.1 to 0.2 unit per cubic centimeter with only one instance in which a level of less than 0.1 unit per cubic centimeter was found. The highest levels were found in the three-week to nine-month and in the thirteen-month to five-year age groups. These two groups received the largest amount of penicillin relative to body weight. Clinical therapeutic results were in no manner different from those obtained in similar groups of patients treated in the usual manner with regular crystalline penicillin.

TABLE III. SUMMARY OF PENICILLIN TITERS IN FORTY-ONE PATIENTS TREATED WITH DURACILLIN

NO.	WEIGHT (KG.)	AGE	PENICILLIN (UNITS)	SERUM TITERS UNITS/C.C.	
				12 HOURS	24 HOURS
12	3.1 to 8.0	3 weeks to 6 months	150,000	1.0 to 4.0	0.2 to 1.0
7	6.9 to 10.8	7 months to 12 months	150,000	0.2 to 2.0	0.1 to 0.2
14	10.1 to 18.8	13 months to 5 years	300,000	1.0 to 2.0	0.1 to 1.0
8	18.8 to 31.5	5½ years to 9 years	300,000	0.2 to 0.5	<0.1 to 0.5

A total number of injections in this series was 320. In addition, approximately 1,000 injections have been given to other children in the St. Louis Children's Hospital, the St. Louis City Hospital, and in the outpatient clinics. There has been one case in which a sterile abscess developed. This resolved spontaneously without open drainage. Dr. Virgil Scott[2] has used this material in outpatient treatment of 102 adults with active or latent syphilis. Five of these patients showed definite toxic manifestations. Four had an urticarial or papular skin eruption which was promptly relieved by the administration of Pyribenzamine. The fifth patient had a more severe reaction with nervousness, apprehension, a feeling of tightness in the chest, numbness in the extremities, and headache.

It has been shown by Lief and co-workers[3] that procaine is hydrolyzed both in vitro and in vivo to p-aminobenzoic acid and diethylaminoethanol. As very small amounts of p-aminobenzoic acid are capable of inhibiting the action of a much larger amount of sulfonamide drugs, the question naturally arises as to whether simultaneous administration of procaine-penicillin with sulfonamides might not result in a diminution or total absence of sulfonamide effect. Until this is shown not to be the case, it would seem unwise to give the two drugs simultaneously in the treatment of infections.

In an attempt to settle this point, a group of children were given Sulfamerazine for three days. On the first and third days Sulfamerazine alone was administered but on the second day two injections of procaine-penicillin were given, twelve hours apart. Two blood specimens were obtained each day and tested against a sulfonamide-sensitive test organism. We have been able to show an inhibitory effect on the test organism of sera containing Sulfamerazine. This inhibition in some cases diminished or was lost following the injection of procaine-penicillin even though the colorimetrically determined serum sulfon-

amide levels were unchanged. However, in fifty tests performed on more than thirty sera, results were not consistent, so that other techniques will need to be devised before this phenomenon can be accurately evaluated.

CONCLUSIONS

Procaine-penicillin in the form of Duracillin has been used in both well and sick children. A standard dosage of 150,000 units was given to children under 11 kg. body weight, and 300,000 units were given to children over this weight. Adequate therapeutic serum penicillin titers of 0.1 unit per cubic centimeter or more were obtained in all patients studied twelve hours after injection. In the great majority of patients titers of 0.1 unit per cubic centimeter or more were found twenty-four hours after a single injection.

Injection every twelve hours should be used when high serum titers are desired and every twenty-four hours where a level of approximately 0.1 to 0.2 unit per cubic centimeter is sufficient.

Because of very rapid absorption with peak serum titers one-half to one hour after injection, it is not necessary to give an initial dose of plain crystalline penicillin.

As long as there is a possibility of inhibition of sulfonamides by p-aminobenzoic acid derived from the procaine, it is felt that plain crystalline penicillin should be used in the more severe infections where the sulfonamide drugs must be concomitantly employed.

Undesirable toxic reactions in children are very infrequent. No evidence of sensitization to either penicillin, sesame oil, or procaine was seen. One instance of sterile abscess formation was encountered. This lack of generalized toxic reactions in children is sharply contrasted to the reactions seen in a group of adults similarly treated, where five out of 102 patients showed evidence of sensitization. In these patients, Pyribenzamine successfully relieved the allergic manifestations, and at a later date when given prophylactically prior to subsequent injections of procaine-penicillin, no allergic reactions were observed.

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PATHOLOGIC FINDINGS IN THE NEONATAL PERIOD

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ALTHOUGH approximately 5 per cent of all deaths occur during the neonatal period,[1] i.e., the first month of extrauterine life, many pathologists and clinicians have little interest in investigating these deaths. All too often the deaths are attributed solely to prematurity or atelectasis, neither of which is an adequate primary cause of death.[2, 3] This paper is presented in order to emphasize the fact that an adequate cause of death can be demonstrated in the majority of infants dying within the first month of life. This has been repeatedly demonstrated[4-6] but is still not generally appreciated.

The material for the present paper consists of the consecutive autopsy records of 50 live-born infants dying on the Tulane Service of the Charity Hospital of Louisiana at New Orleans. Infants weighing less than 500 Gm. at the time of delivery were excluded. Fourteen infants were previable premature infants (weight, 500 to 999 Gm.), 23 were viable premature infants (weight, 1,000 to 2,499 Gm.) and 8 were full-term infants (weight 2,500 grams or more). Their ages varied from 5 minutes to 25 days; 33 died within 24 hours of delivery; only 9 lived 7 days or more. Forty infants were Negro and ten were white. An adequate cause of death was demonstrated in 43. Asphyxia was responsible for ten deaths, intraventricular hemorrhage for 10, bronchopneumonia for 7, congenital syphilis for 5, congenital anomalies for 4, and miscellaneous lesions were held accountable for the death of 7 infants (Table I).

TABLE I

CAUSE OF DEATH	CASES
Asphyxia	10
Intraventricular hemorrhage	10
Bronchopneumonia	7
Miscellaneous	7
Undetermined	7
Congenital syphilis	5
Congenital anomalies	4
Total	50

Eight of the ten infants who died as a result of asphyxia were premature. One infant lived for twenty-seven hours, all of the others died in less than one day. The gross findings at autopsy in an infant dying of asphyxia consist of multiple petechiae and marked venous congestion.[6] In the present series the diagnoses have all been confirmed by microscopic examination. The histologic diagnosis of asphyxia is based on the presence of large amounts of amniotic sac contents in the pulmonary alveoli. These appear free in the alveoli as blue or, less often as pink, elongated, fusiform and twisted cornified epithelial cells, usually non-nucleated, derived from the skin of the fetus (Fig. 1). At

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other times, and especially in premature infants, a pink hyaline material may be present as a distinct membrane applied to the alveolar surfaces (Fig. 2); this material is thought by some to be vernix caseosa.[6, 7] Occasionally lanugo hairs or meconium may be present within the pulmonary alveoli.

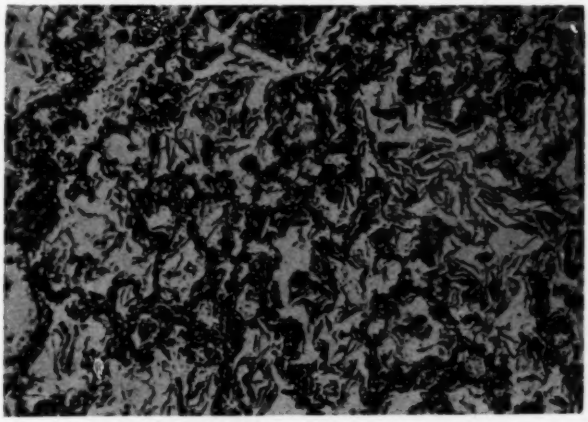

Fig. 1.—Lung showing large numbers of cornified epithelial cells in the alveolar spaces (×175).

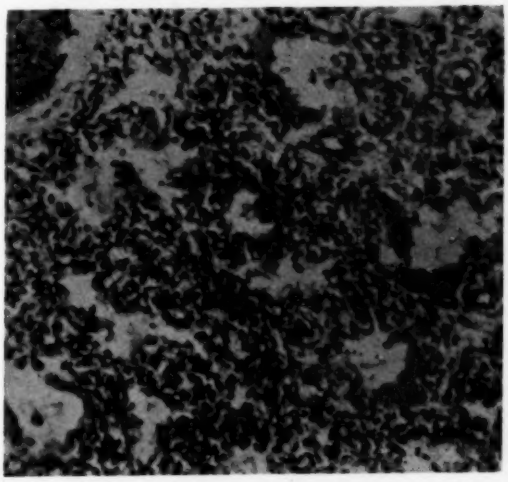

Fig. 2.—Lung showing asphyxial membrane (×175).

The presence of amniotic sac contents within the alveoli of the lungs is a result of intrauterine respiration. Whether such respiration occurs under normal circumstances or whether it is dependent upon intrauterine asphyxia is a moot question.[8-11] However, regardless of the presence or absence of normal intrauterine respiratory movements, most authors agree that the presence of large amounts of amniotic debris within the lungs is indicative of fetal asphyxia.[6, 12]

Intraventricular hemorrhage was responsible for ten deaths. All but one infant in this group were premature, seven of these infants weighed less than 1,300 grams. Macgregor[6] believes that intraventricular hemorrhage in the neonatal period occurs almost exclusively in premature infants. The duration of life in these ten infants varied from 5 minutes to 31 hours; only three lived over 17 hours. In one infant the amount of intraventricular hemorrhage was slight but there was a massive subarachnoid hemorrhage.

The mechanism of production of these hemorrhages is not clear, and Holland[13] has commented on the difficulty of differentiating those caused by asphyxia from those of traumatic origin. The hemorrhage within the ventricles may arise from engorged choroid plexuses or it may follow rupture of a subependymal hemorrhage into the lateral ventricle. These subependymal hemorrhages may attain considerable size, and are usually located about the terminal vein between the caudate nucleus and the thalamus (Fig. 3). Knowledge of these subependymal hemorrhages is important to the clinician handling newborn infants, as improper care may possibly convert a relatively innocuous subependymal hemorrhage into a fatal intraventricular hemorrhage.

Fig. 3.—Coronal section through cerebral hemispheres showing bilateral subependymal hemorrhages.

Bronchopneumonia was held responsible for seven deaths in the present series. All of these infants were premature, their weights ranging from 885 to 2,470 grams. Their ages varied from 17 minutes to 24 days, and four of them lived less than 24 hours. Fourteen other infants had varying degrees of bronchopneumonia, but in these it was not thought to be the principal cause of death. Bacteriologic studies were not carried out as most of the infants had died at least forty-eight hours before the autopsy was performed. The infants dying of bronchopneumonia within the first twenty-four hours after birth probably represent examples of antenatal infections.[14, 15] It has already been pointed out that intrauterine respirations may occur, particularly in asphyxi-

ated fetuses, and that these may lead to the aspiration of amniotic sac contents. If the contents of the amniotic sac are infected, as they may be after premature rupture of the membranes, an intrauterine pneumonia may occur. The importance of pneumonia as a cause of death in the neonatal period has been pointed out by others. Macgregor[16] found inflammatory changes in the lungs of 37 per cent of live-born infants surviving up to 28 days and Benner[15] noted inflammatory reactions in the middle ears, sinuses or lungs of 46 per cent of live-born infants dying under the age of 2 days.

Congenital syphilis was responsible for five deaths in the present series. All were premature Negro infants; one lived for 34 hours, and the others died in less than one day. They showed the usual lesions of congenital syphilis, including hepatomegaly, splenomegaly, syphilitic osteochondritis, and syphilitic pancreatitis. One infant presented the clinical picture of hemorrhagic disease of the newborn and one showed syphilitic involvement of the hypophysis.[17] Four of the five infants showed what appeared to be a nonspecific bronchopneumonia. Chase[18] believes that aspiration pneumonia following intrauterine asphyxia is the immediate cause of death in the majority of syphilitic infants who die before the age of one month.

Congenital anomalies were held responsible for the death of four infants. The anomalies were atresia of the bowel, meningomyelocele with associated meningitis, anencephaly, and external hydrocephalus. The latter was associated with congenital absence of the tectum of the midbrain. Fraser and Dott[19] have described two cases of external hydrocephalus associated with congenital absence of the quadrigeminal plate, the superior cerebellar peduncles, and the posterior wall of the aqueduct of Sylvius, with resultant discharge of cerebrospinal fluid directly from the ventricles into the "submeningeal space." The anencephalic infant lived for two days and showed hypoplasia of the adrenals and aplasia of the pars nervosa of the hypophysis, as described by Angevine.[20]

The miscellaneous lesions responsible for death included thromboses of the venous sinuses of the dura mater (three cases), dural tears (two cases) and meningitis (two cases). These infants lived from 2 hours and 11 minutes to 18 days; five of them lived 7 days or more.

DISCUSSION

Both clinicians and pathologists should recognize the fact that an adequate cause of death can be demonstrated at autopsy in the majority of infants dying during the neonatal period. Careful postmortem examinations are especially important during this period, when clinical diagnoses are so unreliable.

The high incidence of infection in the present series is noteworthy. Of the fifty infants, some form of infection (bronchopneumonia, congenital syphilis, meningitis, or omphalitis) was present in twenty-five infants, and in fourteen infection (bronchopneumonia, congenital syphilis, or meningitis) was thought to be the primary cause of death. The importance of infections as a cause of neonatal deaths has been emphasized by others but is still not generally appreciated. A clinical diagnosis of many of these infections would be impossible,

but recognition of the fact that infections are common in the neonatal period, occurring even in infants shortly after birth, should aid in lowering neonatal mortality rates.

SUMMARY

An adequate cause of death was demonstrated at autopsy in forty-three of fifty infants dying during the neonatal period. Asphyxia, intraventricular hemorrhage, and bronchopneumonia were the leading causes of death. Twenty-five of the fifty infants showed inflammatory lesions which, in most instances, were attributable to infection, but in only fourteen of these was infection believed to be the principal cause of death.

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THE TREATMENT OF AMMONIA DERMATITIS WITH DIAPARENE

Report on 500 Cases

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IN A preliminary report[1] we suggested the use of a quarternary ammonium compound, para di-isobutyl-eresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate* for ammonia dermatitis. This method of treatment was based on Cooke's[2] pioneer work, which demonstrated that the ordinary diaper rash is usually an ammonia dermatitis and that "the cause of the ammonia production is directly due to bacterial decomposition of urinary urea into free ammonia, and the principal organism concerned is *B. ammoniagenes,* a saprophytic, gram-positive bacillus which originates in the feces and infests the skin of the diaper region." Cooke further pointed out that "the prevention and treatment of ammonia dermatitis is dependent on preventing bacterial growth, and this is readily accomplished by the use of a nonvolatile antiseptic in the diaper itself."

We reported that para di-isobutyl-eresoxy-ethoxy-ethyl di-methyl benzyl ammonium chloride monohydrate has a marked bactericidal action on *B. ammoniagenes.* Forty-nine out of fifty infants with ammonia dermatitis were cleared within one week by impregnating their diapers with this drug. In a series of tests we were unable to produce any toxic or allergic effects on the skin with solutions of this drug.

We have now reviewed the first 500 cases which were diagnosed as ammonia dermatitis and then treated with Diaparene-impregnated diapers. One tablet to two quarts of water provided an approximately 1:25,000 solution. Up to six diapers were placed in a basin and the solution poured over them. This procedure, if carefully followed, insures approximately equal concentration in each diaper. The drug is absorbed from the solution by the diapers almost quantitatively, irrespective of the concentration of the solution. If the diapers were introduced one at a time, the drug might be absorbed on the first diaper placed in the solution.

Tables I and II give evidence that diapers treated in this fashion are bacteriostatic against *B. ammoniagenes* and *Staphylococcus aureus.* All treated diapers, even after ironing and storage, inhibited the growth of these organisms. Furthermore, samples of all these treated diapers, when incubated in glucose broth for twenty-four hours, showed no growth.

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*This drug was supplied to us as Diaparene tablets by Homemakers Products Corp., New York, N. Y.

TABLE I. EXTRACT AGAR DEEP INOCULATED WITH TWENTY-FOUR-HOUR BROTH CULTURE STAPH. AUREUS (44) 0.1 C.C. PIECE OF TREATED DIAPER, 1 CM. SQUARE, PLACED ON SURFACE

DIAPERS	ZONE OF INHIBITION		
	A	B	C
3 treated diapers (A, B, C)	+	+	+
3 treated diapers (A, B, C) ironed	+	+	+
3 treated diapers (A, B, C) after storage for two weeks	+	+	+
3 untreated diapers (controls)	0	0	0

TABLE II. EXTRACT AGAR INOCULATED WITH A CULTURE OF B. AMMONIAGENES (ALKALIGENES AMMONIAGENES) 0.1 C.C. PIECE OF TREATED DIAPER, 1 CM. SQUARE, PLACED ON SURFACE

DIAPERS	ZONE OF INHIBITION		
	A	B	C
3 treated diapers (A, B, C)	+	+	+
3 treated diapers (A, B, C) ironed	+	+	+
3 treated diapers (A, B, C) after storage for two weeks	+	+	+
3 untreated diapers (controls)	0	0	0

RESULTS

We have analyzed the results in 500 cases of diagnosed ammonia dermatitis treated with Diaparene. These cases include hospitalized, clinic, and private patients. All rashes were in the diaper region and there was an associated ammonia odor reported in the diapers. They were divided into mild, moderate, and severe rashes. Erythema was called mild, papulovesicular and pustular lesions were called moderate, and ulcerations were denoted as severe. Of the rashes, 172 were called mild; 204 were called moderate; and 124, severe. Of these infants, 87 also had ulcerations of the external urethral meatus.

Of the cases, 436 which were diagnosed as ammonia dermatitis and treated with Diaparene, cleared promptly within one week. Of the sixty-four which did not clear, forty-three were mild, sixteen were moderate, and three were severe rashes. All but three of the infants with ulcerations of the external urethral meatus were cleared.

Nine of the sixty-four did not return or refused further treatment. The remaining fifty-five failures were reviewed. Twenty-three of these were thought not to have been ammonia dermatitis, but due to irritative or allergic factors. In eleven of these the mother had not prepared the diapers according to instructions. In the other twenty-one cases, we could find no reason for the failure.

COMMENT

Ammonia dermatitis is the most common rash in the diaper region but there are other possible rashes which may occur in that area. Some of these which confused us were contact dermatitis, atopic dermatitis, acid fecal irritation, and intertrigo. Contact dermatitis was often due to soap, baby oil, and bleach in the diaper. Atopic dermatitis was blamed on the usual milk, wheat, egg, and orange juice. Acid fecal irritation was associated with loose stools and was most marked about the anus. Intertrigo was found in fat babies and was most marked in the folds of the skin. Occasionally it is difficult to differentiate between these and ammonia dermatitis. We have found it practical,

when in doubt, to give a therapeutic trial with Diaparene, since ammonia dermatitis is the most frequent offender. If this fails, we then go into the laborious investigation of the various kinds of contact and atopic dermatitis.

The severe cases of ammonia dermatitis have been secondarily infected with *Staph. aureus* and various streptococci. In these cases best results are obtained by using triple strength Diaparene (three tablets to two quarts of water). In vitro, this stronger concentration has a marked bactericidal action on these organisms.

We have received communications from a few pediatricians who feel that boric acid is still the treatment of choice for ammonia dermatitis. Boric acid is a very weak bactericide and there are many reports[3] of poisoning when applied to the broken or burned skin. We feel that it has outlived its usefulness and should be discarded.

In the past we have followed Cooke[2] in using a 1:4,000 solution of mercuric chloride to impregnate the diapers in ammonia dermatitis. It is an efficient bactericide against *B. ammoniagenes* but has well-known poisonous properties. Our results with Diaparene reveal an even greater efficiency, and, thus far, with no irritant or allergic effects on the skin.

It is of great importance, in using this preparation, to instruct mothers to follow directions carefully. In one case reported to us, the mother by mistake gave her infant orally one tablespoonful of the solution three times daily for one month. Although there were no apparent harmful effects, such accidents emphasize the importance of careful directions on the part of the physician.

SUMMARY

1. A review has been made of 500 cases of diagnosed ammonia dermatitis treated with Diaparene-impregnated diapers.

2. This has proved a safe and efficient treatment for ammonia dermatitis.

3. Other rashes occur in the diaper region which may be confused with ammonia dermatitis. Some of these are due to contact dermatitis, atopic dermatitis, acid fecal irritation, and intertrigo.

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THE PREVALENCE OF COLDS IN NURSERY SCHOOL CHILDREN AND NON-NURSERY SCHOOL CHILDREN

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WHETHER or not there is an actual health risk in the daily exposure of the pre-school child to groups of people, adults or his peers, is frequently a question of debate. This study represents an attempt to evaluate certain effects of group exposure in a nursery school situation. In selecting a certain aspect of health for study, it was decided to measure the prevalence of colds in nursery school and non-nursery school children, because colds represent the largest single cause of school absenteeism at various age levels. Another reason for measuring colds is that they are transmitted by the discharges of the respiratory tract, as are the other common communicable diseases. The control of the common cold is fundamental in any program of disease control in the schools.

In selecting a definition of a cold to be used in this study, various possibilities were considered. Hilding[6] defined the cold as a "widespread, mild, afebrile rhinitis characterized by a copious, thick, mucinous, nasal discharge, and a self-limited course of two to three days." McGee, Andes, Plume, and Hinton[8] regard the cold as a "symptom complex" which may follow irritation of the nose and throat by chemical agents, physical agents, or by infection. In this study the definition given by McGee, Andes, and associates was followed, since no method was available to differentiate factors causing upper respiratory inflammations.

PROCEDURE

Subjects.—The subjects of this study were twenty-five children attending the Purdue University Nursery School and twenty-six children not attending the nursery school whose names had been placed by their parents on its waiting list. All children enrolled from Jan. 15 through April 8, 1946, were to be included. However, due to moves to other cities, frequent or long absences as a precautionary measure, inadequate records, and extended vacations in a different climate, seven of the total enrollment in the nursery school and six of the original thirty-two in the non-nursery school group were omitted from the final study.

The nursery school children were in attendance from 9:00 A.M. to 12:45 P.M. for five days a week. Upon arrival at school each child was checked for any signs of illness by a registered nurse. It was the policy of the school to exclude all children with symptoms such as red, watery eyes, nasal discharge, overfatigue, and/or unusual irritability. If such signs of illness developed during school, the child was isolated or was sent home.

The nursery school children who served as subjects in this study ranged from 29 to 56 months of age. The group consisted of thirteen girls and twelve

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boys. As is usual in this type of nursery school, the subjects tended to be above average in intelligence and to come from homes of a relatively high socio-economic level. Twenty had fathers who were in professions and five had fathers who were in business. All but three of this group of children were taking vitamin compounds in some form in addition to their regular diet. Six children were known to have definite allergies and five others had shown allergic manifestations of some type and in various degrees. All of the nursery school children had had a physical examinations by the family physician within the eighteen months preceding the study. The health status of twenty-three was rated as "superior" and of two as "average" by the physician. Fourteen children of this group had been to the dentist at least once for filling of cavities, teeth cleaning, or dental checkup.

The non-nursery school children who served as subjects in this study ranged in age from 23 to 52 months. The group consisted of ten girls and sixteen boys. The subjects came from homes of relatively high socio-economic level. Of this group, twenty had fathers who were professional men and six had fathers who were businessmen. All but two of this group were taking vitamin compounds in addition to their regular diet. Three of these children were known to have definite allergies and seven had shown allergic manifestations of some type and in various degrees. All but three had had a physical examination by the family physician within the eighteen months preceding the study. The health status of twenty-three was rated as "superior" by the family physician. Five children of this group had been to the dentist at least once for teeth cleaning, filling of cavities, and dental checkup. The non-nursery school group was selected from the nursery school waiting list on the basis of age. It was possible to pair each nursery school child with one in the non-nursery school group who had a birthday within six months of his. For both groups, the amount of association with other children in the family and other groups such as Sunday school seemed similar.

Methods.—After study of literature concerning colds, a list of symptoms indicating the presence of upper respiratory infection was constructed. This list was then revised and all medical terms changed to their lay equivalents. Care was taken to use terms in common usage and to reduce the list as far as possible but to maintain a detailed report of the cold.

To further validate the symptom check list, three physicians in active practice locally were interviewed. All were in agreement as to the terms used, that the list would give a detailed report of colds and that red, watery eyes, nasal discharge, mild loss of appetite, restless sleep, and headache are symptomatic of a cold. Two physicians also considered conduct changes such as irritability, listlessness, and rather inactive play as an important part of the diagnosis, particularly when endeavoring to differentiate infectious rhinitis from that of allergic origin. To be assured of the list's practicability in use, three mothers used it when their children had colds. All agreed that the list was understandable and easy to use. The symptom check list was then considered ready for use. The items included are listed in Fig. 3.

The mothers of every child were interviewed personally. Information was secured by the use of a questionnaire. All of the mothers of those two groups expressed interest and cooperated willingly in the study. The mothers were asked to keep a record of the number and severity of the child's colds by using the symptom check list for a period of ten weeks, Jan. 28, 1946, to April 8, 1946. At least once during this time each mother was contacted by telephone or personally; this served as a reminder of the study. At the close of the ten-week period the symptom check lists were collected by mail or personally through a home visit.

RESULTS

Prevalence of Colds in Relation to Certain Variables.—

1. Prevalence of cold in relation to nursery school attendance: The individual child's total cold score was obtained by adding all the symptoms that were checked during the ten-week period. This score served as a measure of the cold to be related to different variables. Table I shows the comparative total cold scores for the twenty-five nursery school children and the twenty-six non-nursery school children.

TABLE I. COMPARISON OF TOTAL COLD SCORES OF NURSERY SCHOOL AND NON-NURSERY SCHOOL CHILDREN, JAN. 28—APRIL 8, 1946 (TOTAL COLD SCORE = TOTAL NUMBER OF SYMPTOMS)

	RANGE	MEAN	STANDARD DEVIATION	MEDIAN	QUARTILE 3	COMPOSITE T-SCORE
Nursery school, N = 25	0-168	38.7	42.6	38	43.5	50.2
Non-nursery school, N = 26	0-123	37.3	32.86	20	59.3	49.2
Total N = 51	0-168	38.0	33.0	24.4	57.6	49.7

A few scores in each group were at the extreme ends of the distribution. Lindquist[7] says these scores receive an automatic weighting in proportion to the size of the standard deviation when the mean is taken. The composite T-score was used as a means of comparison because it removes this weighing. Lindquist defines the T-score as an arbitrary scale with a mean of 50 and a standard deviation of 10. The non-nursery school group had several low total cold scores shown by a median of 20 but quartile 3 of the distribution is 59.3, which shows a wide scatter. The mean difference is 1.4. As chance alone would account for a difference of this size 22.4 times out of 100, it cannot be said that the non-nursery school children had fewer or less colds than the nursery school children. The difference between the composite T-scores, 50.2 and 49.2, was slight. No significant difference existed between the two groups in the total number of cold symptoms in this ten-week period.

Fig. 1 shows the number of colds that each group had during the time of the study. Sixteen children in each group had one cold or more during the study. Seven of the nursery school group and ten of the non-nursery school group had two or three colds during the time of the study. Two of the nursery

school children had four colds during the study but none of the non-nursery school group had four colds during the ten-week period. The nursery school group averaged 1.5 colds and the non-nursery school group 1.3 colds during the study; the T-score device revealed no significant difference between the two groups in the number of colds.

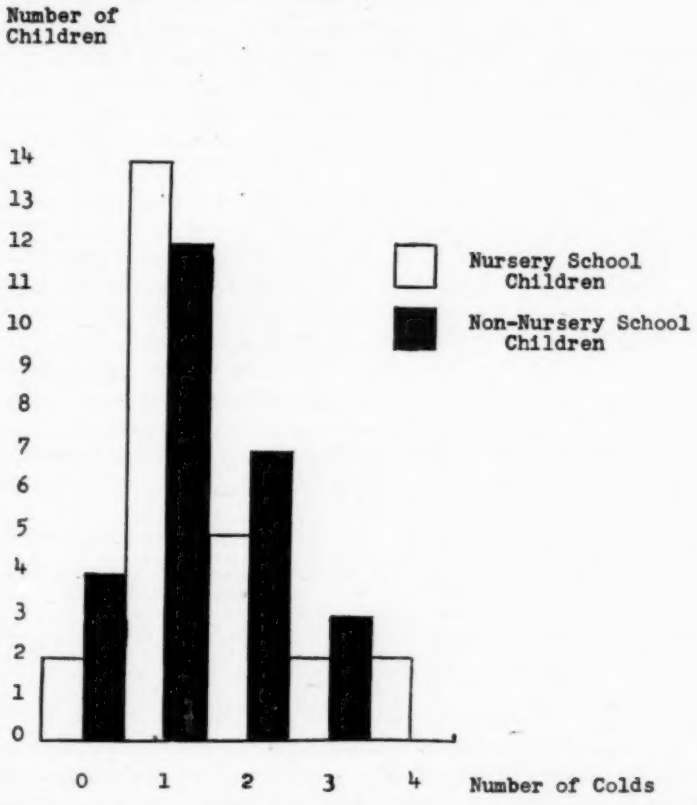

Fig. 1.—Comparison of the number of colds of nursery school and non-nursery school children, Jan. 28 to April 8, 1946.

To consider the severity of each cold, the total cold score of each child was divided by the number of colds he had during the time of the study. Table II shows a comparison of the severity of colds between nursery school and non-nursery school children. The nursery school children had an average cold score of 20.5 for each cold per child. The non-nursery school group showed an average cold score of 24.1 for each cold per child. The T-score was utilized to remove the automatic weighting of the scores at the extreme ends of the distribution. The composite T-score of 49.2 for the nursery school children and of 50.7 for the non-nursery school children shows a difference too slight to be

significant, as it would occur 51.6 in 100 by chance alone. Severity of colds was similar in the two groups.

TABLE II. COMPARISON OF SEVERITY OF EACH COLD OF NURSERY SCHOOL AND NON-NURSERY SCHOOL CHILDREN, JAN. 28—APRIL 8, 1946
(AVERAGE COLD SCORE FOR EACH CHILD)

	RANGE	MEAN	STANDARD DEVIATION	MEDIAN	QUARTILE 3	COMPOSITE T-SCORE
Nursery school N = 25	0- 74	20.5	16.3	15	24.75	49.2
Non-nursery school N = 26	0-123	24.1	24.1	18	25.0	50.7
Total N = 51	0-123	22.4	21.5	15.7	25.0	50.5

2. Prevalence of colds in relation to age: To determine the relationship of age and prevalence of colds, the children were considered as one group of fifty-one subjects. There were six children in the combined groups who had no colds during the time of the study. The children were grouped in age ranges of one year. Table III shows the prevalence of colds in relation to age. Children ranging from 23 to 35 months in age comprised 25 per cent of the total group; they included 24 per cent of the total number of children who had colds and had 25 per cent of all the colds suffered by the total group. Similar per cents at this age level and the other two of the one-year age grouping indicate similarity in the prevalence of colds at the various age levels of pre-school children.

TABLE III. PREVALENCE OF COLDS IN RELATION TO AGE, JAN. 28—APRIL 8, 1946

AGE OF CHILDREN IN MONTHS	NUMBER OF CHILDREN N = 51	PERCENTAGE OF TOTAL GROUP OF CHILDREN N = 51	PERCENTAGE OF TOTAL GROUP WHO HAD COLDS N = 45	PERCENTAGE OF ALL COLDS IN TOTAL GROUP N = 73	PERCENTAGE OF TOTAL GROUP WHO HAD NO COLDS N = 6
48 to 59	11	22	24	18	0
36 to 47	27	53	51	57	5.4
23 to 35	13	25	24	25	2.6

3. Prevalence of colds in relation to the number of people living in the home: The nursery school children and the non-nursery school children were grouped according to the number of people living in the home and the number of colds suffered during the study. Information regarding this variable is included in Table IV. Children living with two or three people at home in addi-

TABLE IV. PREVALENCE OF COLDS IN RELATION TO THE NUMBER OF PEOPLE LIVING IN THE HOME, JAN. 28—APRIL 8, 1946

NUMBER OF PEOPLE LIVING IN THE HOME	NUMBER OF CHILDREN			MEAN NUMBER OF COLDS PER CHILD		
	NURSERY	NON-NURSERY	TOTAL	NURSERY	NON-NURSERY	TOTAL
7-12	1	2	3	0	1.0	1.0
6	5	3	8	2.0	1.0	1.5
5	3	7	10	1.0	1.6	1.3
4	5	7	12	0.8	1.6	1.2
3	11	7	18	1.8	1.4	1.6

tion to themselves averaged 1.6 or 1.2 colds during the study. The children with four or five people in the home other than themselves averaged 1.3 or 1.5 colds during the study. Children with six to eleven people living at home in addition to themselves averaged 1.0 cold during the study. The mean number of colds varied only from 1.0 to 1.6. The differences are neither wide enough nor consistent enough to show significant relationship between the prevalence of colds and the number of people living in the home.

4. Prevalence of colds in relation to diet: Numerical diet ratings derived from the scale of Chaney and Ahlborn[4] were used to compare nursery school and non-nursery school children. To equalize the weighting given to individual scores when averaging a distribution, the T-score was again utilized. Table V shows the comparison of diet ratings of the nursery school and non-nursery school groups. The nursery school children had a mean diet rating of 83.4 and the non-nursery school children a mean diet rating of 77.5. The difference between the means is 5.9. As a difference of this size would occur by chance only three times in 100, it is considered to be a reliable one with something beside chance in operation. Furthermore, the composite T-score for the nursery school group was 52.2, whereas that for the non-nursery school group was 46.8. Diet scores of the nursery school children were significantly higher than those of the non-nursery school children.

TABLE V. COMPARISON OF DIET RATINGS OF NURSERY SCHOOL AND NON-NURSERY SCHOOL CHILDREN, JAN. 28–APRIL 8, 1946

	RANGE	MEAN	STANDARD DEVIATION	MEDIAN	QUARTILE 3	COMPOSITE T-SCORE
Nursery school N = 25	60-97	83.4	8.7	84.5	88.1	52.2
Non-nursery school N = 26	55-90	77.5	8.3	79.7	83.6	46.8
Total N = 51	55-97	80.3	8.5	82.2	86.1	49.4

Using the Pearson product-moment method of correlation, the relationship between the diet rating and the total cold score (total number of symptoms shown) was determined for the total group of nursery school and non-nursery school children. The coefficient of correlation was $-.11 \pm .09$, which shows no significant relationship between diet rating of these subjects and total cold score. All but two of the diet ratings showed adequate nutrition.

5. Prevalence of colds in relation to weather: To determine possible relationship between the prevalence of the common cold and weather, the ten weeks of the study were divided into two-week intervals and the number of colds occurring in each interval tabulated. The records of the temperature and humidity for Jan. 28 through April 7, 1946, were obtained from the weather station of Purdue University. In correlating temperature and the prevalence of colds the coefficient *epsilon* was calculated and found to be $.52 \pm .02$. The coefficient *epsilon* was used because Peters and and Van Voorhis[9] say of it, "epsilon has a standard meaning, free from bias and independent of the size of

the sample and of the number of classes into which the sample is divided." The correlation obtained (.52) is larger than the one significant at the one per cent level. Therefore, it is highly probable that there is some relationship between temperature and the prevalence of the common cold. This relationship is shown in Fig. 2. As temperature increased, the number of colds decreased. The relation of humidity to colds was not distinct.

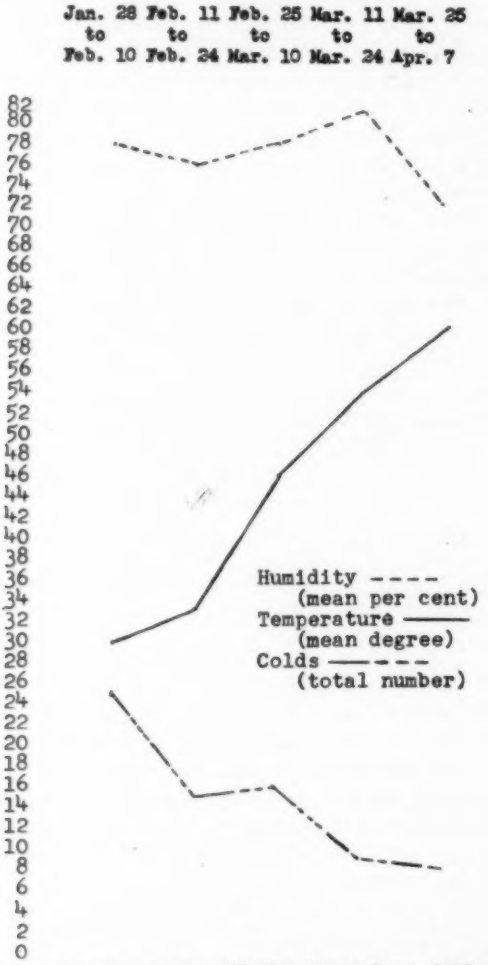

Fig. 2.—Relation of weather to the common cold (for seventy-three of fifty-one children, Jan. 28 to April 8, 1946.)

Most Frequent Symptoms of Colds in Children of Pre-School Age.—

Fig. 3 reveals the most frequent symptoms of colds in children of pre-school age who were included in this study. It shows that a pre-school child

with a cold had either a thin or thick nasal discharge, a mild cough, mild loss of appetite, and red, watery eyes; he was inclined to be irritable and chose rather inactive play. These symptoms which appeared are in basic agreement with those listed by the three physicians, whose opinions were sought in constructing a symptom check list as symptomatic of colds.

Fig. 3.—Frequency of cold symptoms (in seventy-three colds of fifty-one children, Jan. 28 to April 8, 1946).

Comparison of Colds in Same Child.—

In 1947 nine of the children who were previously studied as members of the non-nursery school group entered nursery school. For these nine it was possible to compare the number and length of colds of the same child when he was not attending nursery school and when he was in attendance. Table VI shows this comparison for nine children.

TABLE VI. COMPARISON OF COLDS IN SAME CHILD NOT ATTENDING NURSERY SCHOOL AND ATTENDING NURSERY SCHOOL

	JAN. 28–APRIL 8, 1946 NOT ATTENDING NURSERY SCHOOL		JAN. 28–APRIL 8, 1947 ATTENDING NURSERY SCHOOL	
INDIVIDUAL CHILD	NO. COLDS	TOTAL NO. DAYS OF COLDS	NO. COLDS	TOTAL NO. DAYS OF COLDS
D. T.	3	15	0	0
A. A.	1	4	2	3
D. S.	1	2	0	0
J. D.	0	0	1	4
B. K.	1	14	2	25*
C. R.	1	5	1	10
M. K.	2	15*	2	11*
K. T.	3	21	2	6†
B. R.	2	12	1	3
Total	14	88	11	62
Average	1.55	6.28	1.22	5.63

*Cold complicated by ear infection.
†Tonsils and adenoids removed Feb. 18, 1947.

These children averaged 1.55 colds while not in attendance at nursery school and 1.2 colds one year later when attending nursery school during the period from January 28 to April 8. There was no reliable difference in the number and the length of colds of the same children when not attending nursery school and when attending. While nine cases are not enough to form a definite conclusion, the figures in Table VI offer further evidence that daily exposure of healthy children to a group that is given adequate health protection does not cause any increase in colds.

CONCLUSIONS

Subjects of this study were fifty-one children between the ages of 23 months and 56 months. All children were above average in health status and from homes above the average socioeconomic level. Twenty-five were attending nursery school and twenty-six were not. The nursery school attended had a positive health policy and endeavored to keep sources of infection at a minimum. The ten-week record of the number and severity of colds was from Jan. 28 to April 8, 1946. The record provided the following findings concerning the prevalence of colds in the children studied.

1. There was no statistically reliable difference in the number and severity of colds suffered by children who attended nursery school and those who did not.
2. Various pre-school age levels showed similarity in the prevalence of colds.
3. No relationship appeared between the prevalence of colds and the number of people living in the home.

4. Children attending nursery school had a significantly higher diet rating than those who did not attend nursery school; both groups had adequate or superior diet ratings. There was no relationship between diet rating and prevalence of colds.

5. Colds decreased in prevalence as the temperature grew warmer. The relation of humidity to the prevalence of colds was not distinct.

6. The most frequent symptoms of a cold were: thin or thick nasal discharge, mild cough, mild loss of appetite, irritability, and rather inactive play.

7. Nine children who were studied as members of the non-nursery school group in 1946 attended nursery school the following year. They had no more colds while attending nursery school than when not attending.

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PULMONARY EMBOLISM IN CHILDHOOD

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IN THE last decade, with advances in the knowledge of anticoagulants and antibiotics, widespread attention has been accorded pulmonary embolism in the adult. Little emphasis has been placed on this condition in children; in fact, it has been generally regarded as very rare.

This study deals solely with pulmonary embolism occurring before the age of 15 years. Pulmonary thrombosis, a related disease usually associated with infection, especially measles, is excluded.

REVIEW OF THE LITERATURE

Among earliest reports of pulmonary embolism in childhood is that of Löschner[1] in 1861. He described the case of a 9-year-old boy with a three-day illness characterized by pain and edema in the left leg and delirium. At necropsy there was thrombosis of the left femoral, popliteal, and anterior tibial veins. Death was caused by pulmonary embolism arising from this source. It was believed that phlebitis followed trauma, and, in turn, initiated thrombosis.

A similar case was reported by Curtin[2] in 1878. A 2-year-old child developed severe pain on the inner side of the right leg just below the knee twenty-hours after a fall. The leg became greatly swollen and discolored; the foot was everted. Death occurred three days later. At necropsy the vein at the site of injury was occluded by blood clot. Multiple emboli produced numerous infarcts in the lungs, some fresh, others the seat of necrosis.

Péhu and Horand[3] described an instance of embolism in a 6-year-old boy following otitis media, complicated by mastoiditis and suppurative thrombophlebitis of the right lateral and occipital sinuses and the internal jugular vein. Suppurative pulmonary infarcts were caused by septic emboli from the jugular vein. Guillemot's report[4] was of a similar case in an infant 7 months of age.

In an autopsy analysis Rupp[5] listed eleven instances of fatal pulmonary embolism under the age of 10, and seventeen between the ages of 10 and 20 years. Of these, three cases occurred at 1 year, five at 2 years, and three at 9 years. Little specific information was given regarding the cause of embolism in these children; all followed a severe exhausting illness with involvement of the heart, lungs, or kidneys.

Another case was described by Wessén[6] in a 4-year-old boy following a rib resection for empyema. Six days after operation the patient died suddenly while drinking milk. At autopsy there was a large embolus at the bifurcation of the left pulmonary artery extending into the middle lobe; the pulmonary trunk was free from embolus. The site of the original thrombus was not located, although the iliac arteries and the inferior vena cava were searched; an origin from the right side of the heart was considered.

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There was an additional case[7] in a 9-year-old boy following rheumatic carditis. The right atrium contained a large, firmly attached clot which extended into the pulmonary artery; the lower lobe of the right lung was infarcted. Of interest was the fact that the child was apparently well until twelve hours before death.

Two instances of fatal pulmonary embolism were reported by Fleischman,[8] both associated with measles. The first was in a 4-year-old girl who died suddenly due to a massive embolus which occluded the pulmonary trunk just above the valve and filled the left pulmonary, as well as part of the right pulmonary artery. Phlebothrombosis was discovered in the femoral and iliac veins. The second case was that of a one-year-old boy who also died suddenly while afflicted with measles. An embolus originating in a thrombosed superior sagittal sinus, was found in the pulmonary trunk.

Stulik and Rust[9] cited a case of fatal pulmonary embolism in a girl aged 11 months, who, for about two weeks prior to death, had had severe diarrhea and vomiting associated with fever. Five hours before death the child showed evidence of severe shock and developed the signs of consolidation in the right lung. At autopsy it was learned that both right and left pulmonary arteries were occluded, as were some of the smaller radicles. The origin of the emboli was not determined but was assumed to be in the veins of the lower extremities.

In another report[10] a female infant 7 months old, following pneumonia at 3 months of age, developed otitis media complicated by mastoiditis. On the eighth postoperative day the infant suddenly became cyanotic with rapid respiration and soon expired. At necropsy organized blood clot occluded the branches of the right pulmonary artery leading to the lower and middle lobes; the latter were collapsed. It was assumed that the emboli arose in thrombosed cranial sinuses.

Two additional cases were presented by Hosoi.[11] The first occurred in a boy aged 8 years with hemolytic staphylococcus septicemia. Multiple septic infarcts of the lungs and septic lesions of the heart and brain were caused by bacterial emboli originating in the sphenoidal and ethmoidal cells. The other case was that of a 6½-year-old girl who developed an abscess following appendectomy for a ruptured appendix. A massive pulmonary embolus caused death; thrombi were found in many subperitoneal veins.

Another case of embolism[12] was that of a 10-year-old boy who fell from a wall, injuring his arm. Vomiting and drowsiness appeared shortly after the injury and recurred intermittently until the time of death, two days later. At necropsy there was a pulmonary infarct occupying the entire right middle lobe. A clot was found blocking the main artery to the affected lobe. The right ventricle contained a pale, firm thrombus attached to the wall.

In an autopsy analysis Prettin[13] listed three cases of fatal pulmonary embolism. These occurred in a 3-year-old girl as a result of "heart failure," and in a 12-year-old boy and a 12-year-old girl following diphtheria.

An unusual case[14] was that of a 21-day-old infant who had been ill only three days with mild fever, dyspnea, cyanosis, and restlessness. The heart was the seat of a congenital anomaly consisting of transposition of the great vessels

and auricular septal defects, as well as of a valvular endocarditis. Small, easily detached thrombi were present on the free margin of the mitral leaflets. Masses of thrombi from this site were found in the pulmonary artery, causing infarction of the azygos lobe of the right lung.

Zuschlag[15] in 1947 presented an analysis of thirty-eight cases of infarction of the lung in children, due either to pulmonary thrombosis or embolism. It was thought that emboli caused infarction of the lung more frequently than pulmonary thrombosis. Data regarding individual cases, however, were not provided.

Most recently Crutcher and Daniel,[16] in an autopsy analysis, listed the case of a one-year-old boy with chronic bacillary dysentery associated with marasmus and anemia. Death was caused by a massive pulmonary embolus, the origin of which was not discovered.

CASE REPORT

Clinical History.—A 9-year-old boy was noticed to be unusually inactive on his birthday (July 24, 1947). In the morning he complained of pain about the left shoulder and in the lower half of the left side of the chest. No fever was noted and his appetite remained good. After an uneventful birthday party the child entered an auto preparatory to going for a ride. When the father arrived he found the child dead.

Subsequently it was learned that the boy had entered the hospital in December, 1946, seven and one-half months previously, because of cough, vomiting, and fever. On the day before this admission the boy became ill while at school; he began to cough, vomited once, and it was noticed that he had a fever. He was found later lying beside the highway, apparently having fainted on the way home from school. The past history was not remarkable.

On admission the child was flushed, febrile, and obviously ill. The eyes were red and watery. Respiration was rapid (35), deep, and labored. Slight redness was noticed about the external nares, and the ala nasae were seen to flare on inspiration. Examination of the heart revealed only a tachycardia (100). No abnormalities were detected in the lungs. In the abdomen slight tenderness was elicited in the right lower quadrant; there were no masses and no rigidity. The extremities were not unusual. There was no evidence of trauma. The temperature was 100.4° F.

X-ray examination of the chest on admission showed a slight increase in the hilus markings of the lungs, but no definite evidence of pneumonia. The white cell count was 32,600 with 73 per cent neutrophiles. Urinalyses were repeatedly normal. A diagnosis of bronchopneumonia was considered, and penicillin and sulfa therapy were instituted.

In the following week cough became more troublesome and abdominal pain and tenderness more marked. It was noticed that the patient complained of pain on extension and lateral rotation of the right thigh. Another x-ray film of the chest taken on the seventh day was unchanged. The temperature remained elevated (101° F.), as did the pulse rate (110). The white blood count now was 12,500 with 69 per cent neutrophiles. On the ninth hospital day the abdominal pain was maximum and was most pronounced over the middle of the right inquinal ligament. In this area also marked prominence of the superficial veins are noted. X-ray films of the pelvis, the upper two-thirds of both femurs, the abdomen, and the lumbar spine failed to reveal any abnormality. By the sixteenth day the findings in the right leg disappeared. About this time, however, the left leg similarly had become painful on movement, and was kept in a position of flexion.

The boy gradually improved under penicillin and streptomycin therapy. He was sent home on the twenty-seventh day with a guarded prognosis although he was feeling well. A final diagnosis was not made, although appendicitis, pelvic osteomyelitis, and retroperitoneal infection had been considered.

Five and one-half months after discharge, in May, 1947 (two months antemortem), the child again became ill. An x-ray film showed consolidation of the lower lobe of the

right lung. Mild pneumonia with pleurisy was diagnosed. The boy appeared to recover rapidly, however, and seemed well until the day of death.

Postmortem Examination.—At autopsy done fifteen hours later, external examination revealed cyanosis of the face as well as marked dilatation of the superficial veins of both thighs and the lower abdomen, especially on the right side. The left thigh was found to be one centimeter greater in circumference than the right. The left leg was externally rotated.

There were 100 c.c. of straw-colored fluid in the left, and 25 c.c. in the right pleural cavity. Striking changes were seen in the lungs. At the apex of the left lung (200 grams) there was a small, moderately firm, hemorrhagic area with a dull pleural surface. A similar but smaller fresh infarct was found in the lower lobe. At the base of the lower lobe of the right lung (170 grams) there was a thick superficial zone of scarring representing an older infarct.

At the root of the pulmonary artery the valve opening was obstructed by a massive embolus, 2.5 cm. long and up to 1.8 cm. in diameter. Similar embolic material was found adherent to the wall of the left pulmonary artery. Well-impacted embolus was present also in the small branches in both upper and lower lobes of the left lung. The friable character of the gray emboli suggested origin from an old, well-organized thrombus.

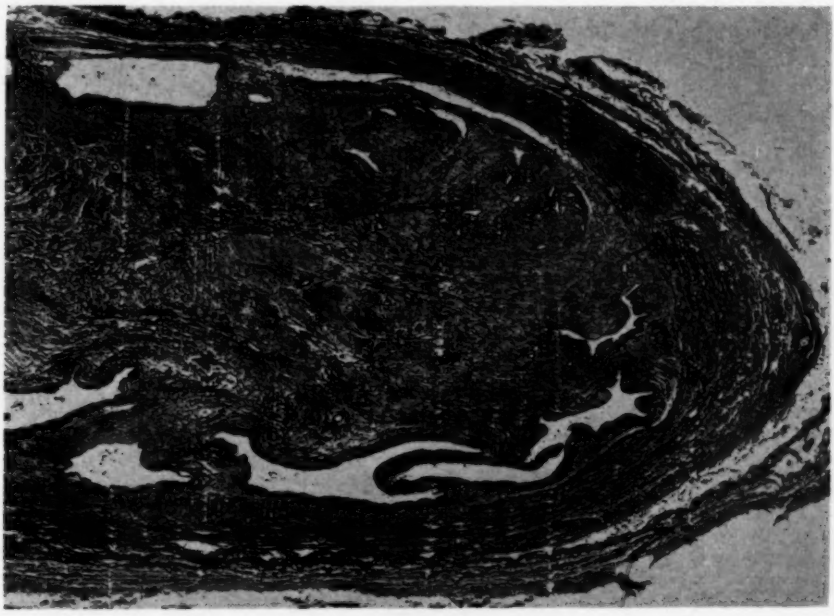

Fig. 1.—Photomicrograph of iliac vein showing striking reduction of lumen by completely organized thrombus (×30).

The source of the emboli was found in the femoral and iliac veins and the inferior vena cava. Spongy yellow thrombus filled the right common iliac vein, and extended into the adjacent portion of the inferior vena cava, the intima of which was considerably roughened. Both external iliac veins and the adjacent portion of the femoral veins were almost completely occluded by confluent bands of connective tissue representing organized thrombus.

Acute dilatation was the only remarkable feature in the heart. In the abdomen there was acute passive congestion of all viscera.

Microscopic examination confirmed the gross findings. The infarcts of the left lung were found to be quite recent; the alveolar walls were still recognizable within the extensive

hemorrhage. The infarct on the right side was considerably older; the alveolar walls were necrotic, and most of the alveoli were partly obliterated by connective tissue.

The material in the left pulmonary artery was firmly attached to the wall by granulation tissue; its composition of vascular collagenous tissue indicated that it antedated the massive embolus at the pulmonary valve. The latter showed no evidence of organization. A section of the iliac vein (Fig. 1) showed the lumen to be replaced almost completely by organized thrombus that was intimately attached to the wall. This thrombus was composed of numerous small blood spaces separated by dense, poorly cellular, collagenous tissue containing many large mononucleated cells laden with hemosiderin. Sections of other organs were not remarkable except for acute passive congestion.

COMMENT

The autopsy findings demonstrated conclusively that the sudden death of the 9-year-old boy was due to massive pulmonary embolism, the embolus arising in partially organized thrombus in the inferior vena cava and the common iliac veins.

The signs and symptoms during hospitalization seven and one-half months before death were undoubtedly those of bilateral thrombophlebitis of the lower extremities. This was indicated by the presence within the femoral and iliac veins of newly formed, fibrous, intraluminal intrusions of thrombotic origin. The cause of the phlebitis was obscure. While it may be postulated that the pulmonary symptoms at that time were those of pneumonia, the thrombophlebitis occurring as a sequel, the possibility of a spontaneous phlebitis cannot be disregarded. There was no history of trauma and the diagnosis of pneumonia was never definitely proved.

The episode of right-sided "pneumonia and pleurisy" two months before death, was the result of minor pulmonary embolism. This was demonstrated by the finding of a healing infarct in the lower lobe of the right lung. The several small, fresh infarcts in the left lung would appear to have occurred early on the day of death.

There would seem to be no doubt that thrombosis developed in the inferior vena cava following the bout of thrombophlebitis of the iliac and femoral veins. From this new site came both the preliminary small emboli and the final massive embolus.

TABLE I. NECROPSY INCIDENCE OF PULMONARY EMBOLISM, WITH SPECIAL REFERENCE TO EARLY AGE DISTRIBUTION

AUTHOR	NO. AUTOPSIES	CASES OF FATAL EMBOLISM		
		ALL AGES	0-9 YR.	10-19 YR.
Rupp[5]	13,000	657	11	17
Hosoi[11]	810	64	2	1
Prettin[13]	2,897	231	1	4
Cruteher and Daniel[16]	2,580	55	1	2
McCartney[17]	9,275	73	0	0
Rosenthal[18]	1,000	2	0	0
Belt[19]	567	56	0	0
Kirshbaum and Shively[20]	10,650	25	0	1
Hunter[21]	351	11	0	0
Neuhof and Klein[22]	5,146	88	0	0
Stevenson and Stevenson	466	20	1	0
Total	46,742	1,282	16	25

DISCUSSION

Composite of several autopsy studies reveals that pulmonary embolism in children and young adults, while not common, occurs more frequently than is generally believed. The available necropsy surveys concerning embolism at all ages are summarized in Table I. Of a total of 1,282 cases of fatal embolism encountered in 46,742 routine autopsies, there were sixteen instances, or 1.25 per cent, in the 0- to 9-year group, and twenty-five, or 1.95 per cent, in the 10- to 19-year group. It must be emphasized that these results represent only the necropsy incidence of pulmonary embolism. The percentage of autopsies in the age groups represented by these cases remains unknown.

Etiology.—Pulmonary embolism in children is confined almost entirely to the nonoperative group. In only two of the thirty summarized cases is embolism known to have followed operation; in both it was thought that preceding infection played the primary role in producing the pre-embolic thrombosis. Infectious disease, generally of an acute variety, antedated embolism in fifteen cases, while chronic debilitating disease, presumably not associated with acute infection, was the basis for embolism in twelve. Trauma was the apparent precipitating factor in only three cases. The primary diseases complicated by embolism are listed below; those of an obscure or doubtful nature are not included.

Diseases complicated by pulmonary embolism included otitis media and mastoiditis, 3; measles, 2; diphtheria, 2; pleural empyema, 1; appendiceal abscess, 1; rheumatic carditis, 1; bacterial endocarditis, 1; bacillary dysentery, 1; septicemia, 1; pneumonia, 1.

The origin of emboli in the infectious group was found in both the systemic circulation and in the heart. Emboli originated in the heart in two cases; both were associated with endocarditis. Thrombophlebitis of the extremities provided the source in three cases and retroperitoneal phlebitis was the cause in another. The source of emboli in five cases, within thrombosed intracranial sinuses, associated either with local or general infection, must be assumed to be a feature peculiar to childhood. The embolic source was not determined in five instances.

It is difficult to assay the role of sex in the causation of pulmonary embolism. Emboli were found in nine boys and six girls; in some cases, however, the sex of the child was not stated.

Pathologic Anatomy.—Only sixteen of the thirty reports of pulmonary embolism provide complete necropsy data. Embolism resulted in infarction in eight cases; of these, the right lung alone was involved in three, and both lungs were affected in five instances. Infarction failed to occur in seven cases. These results correspond closely to the size of the emboli; multiple small emboli were found in nine cases, while a single, massive embolus was discovered in seven instances. Although single infarction was not described in the left lung in any case, it is noteworthy that emboli lodged in the left, as frequently as they did the right pulmonary artery.

In adults thrombosis of the veins of the extremities, subsequent to disease elsewhere in the body, provides the major source of pulmonary emboli. In

Allen's series,[23] in which all age groups were included, 95 per cent of emboli arose in the deep veins of the legs. This is not the situation in children. Of the sixteen childhood cases described completely, thirteen children had thrombosis of the veins within or immediately adjacent areas of infection or trauma. The remaining three are the only known reported instances in children in which thrombosis of the veins occurred at a site unrelated to the primary disease. In the two cases of measles reported by Fleischman,[8] the cranial sinuses and the left femoral and iliac veins, respectively, were involved; the lesion in both was termed phlebothrombosis. In our case thrombophlebitis was present; it could not be determined whether this was primary or secondary.

In addition to these three instances, the only reference to thrombosis of the veins of the extremities in children is provided by Zuschlag,[15] who mentions involvement of the femoral vein in four instances and the iliac vein in an equal number. A search for thrombosis in the deep veins of the legs was performed by Hunter and collaborators[21] in 351 autopsies; it was found in 52.7 per cent of the patients, the youngest of whom was 15 years of age. In Barker's[24] study of primary idiopathic thrombophlebitis the youngest patient involved was 21 years old. Levinson[25] writes that he has encountered only two instances of peripheral thrombophlebitis in children, except for the transient variety following "cut-down" for intravenous therapy. One of his cases was in a 4-year-old child who had femoral thrombophlebitis associated with intestinal lymphosarcoma; the other was due to an infection of the thigh.

Clinical Findings.—The clinical aspect of pulmonary embolism in children is generally similar to that in adults. The majority of patients showed signs and symptoms which, either at the time of the illness or in retrospect, were those suggestive or typical of pulmonary embolism. Undoubtedly some cases were misdiagnosed because the possibility of embolism at an early age was not considered. The most remarkable feature is the frequency with which sudden death occurred. In seven of sixteen cases a single, massive embolus caused sudden death. The fatal embolus in some instances was preceded by smaller emboli, while in others it occurred as a solitary event. In Zuschlag's[15] series, sudden death occurred in 24.4 per cent of children having either pulmonary thrombosis or embolism.

SUMMARY

1. The literature concerning pulmonary embolism in children is reviewed and reference is made to twenty-nine previously reported cases.

2. A case of pulmonary embolism causing sudden death is reported in a 9-year-old boy; emboli arose in thrombosed veins of the extremities.

3. The clinical and pathologic features of childhood pulmonary embolism are discussed; the rarity of peripheral thrombophlebitis in children is emphasized.

Thanks are due Dr. Charles L. Rothschild for furnishing the clinical history, and to Mrs. Grace Brooks for technical assistance.

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DYSGERMINOMA OF THE OVARY IN A FOUR-YEAR-OLD GIRL WITH METASTASES CLINICALLY SIMULATING WILMS' TUMOR AND ADRENAL NEUROBLASTOMA

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DYSGERMINOMA ovarii has not been found listed in modern textbooks of pediatric medicine, surgery, radiology, or in pediatric journals. Nevertheless, in gynecologic and pathologic literature up to 1947, Mazel[5] found 250 cases, Moreton[7] over 300 cases, and Schneider and Vesell[10] more than 300 cases already reported.

Opinion is still divided in the literature in regard to the degree of malignancy, the incidence of bilateral ovarian dysgerminomas, and the nature and advisability of surgical and radiological treatment. In a previous paper on sympathoblastoma,[4] it was mentioned in the differential diagnosis of these adrenal and abdominal tumors. We are inclined to agree with Mazel,[5] that the neoplasm is usually highly malignant, that surgical management logically must be as radical as that of carcinoma of the ovaries, that the neoplasm attacks even the very young and surgeons are tempted to restrict themselves to conservative removal of the tumor and to rely on postoperative radiation, that once the diagnosis is made the most pressing objective is not conservation of potential procreative power but the preservation of life itself.

We have recently been called upon to give postoperative radiation to a 14-year-old girl riddled with metastases who had only removal of the ovarian dysgerminoma and its adjacent tube. The metastases appeared in less than one year after this conservative surgery and she died within six months of the appearance of the metastases. We cannot agree with repeated pleas for conservative surgery in spite of its occasional successes. Radical surgery with panhysterectomy and bilateral salpingo-oophorectomy seem imperative. If tumor remains we do not object, and in fact we favor postoperative radiation therapy to pelvis, periaortic nodes, thoracic duct, and supraclavicular areas similar to that accorded seminomas, but with it we do not expect or promise permanent cure. Moreover, if the possibility of residual tumor remains following radical surgery, we cannot agree with the reasoning that, "we customarily withhold postoperative irradiation because it will permanently sterilize and will prevent the full maturation of the individual. If malignant cells have been left in the operative field, x-rays will probably not destroy all of them; if neoplasm has not been left, x-ray treatment is superfluous and will bring on the detrimental effects of destruction of the remaining ovary." We would repeat Mazel's plea for the most radical surgery, and the most pressing objective is not the conservation of

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potential procreative power but the preservation of life itself. Until postoperative irradiation is given an opportunity following radical surgery, we will not know whether it can destroy the radiosensitive cells in the body sufficiently to preserve or even prolong life.

CASE REPORT

A Negro girl 4 years, 3 months old, was admitted to the hospital with a chief complaint of pain in the epigastrium, nausea, and vomiting of two days' duration. A mass the size of a small lemon was palpated in the left upper quadrant on Dec. 11, 1944, which within three days became the size of a grapefruit. There was a history of a cold in the head which started four weeks previously with sneezing and cough. One week later a purulent sore developed on the leg. The sore broke down and spread to the face, trunk, and extremities. A sulfanilamide ointment was applied with improvement, but at the time of the examination there was persistence of the infection on the skin of the right ear, apparently impetigo contagiosa.

The previous history showed that the father had syphilis four years previously and had received treatment for the disease. The mother had a negative blood Wassermann. The child was born at term, talked at 11 months, and walked at 15 months. The general health had been good until the beginning of the present illness. The patient appeared to have lost 10 to 15 pounds in weight. Beginning Dec. 11, 1944, the patient had been having fever with excessive sweating day and night. Three months before the present illness the patient was pinned under a heavy object which fell on her upper abdomen.

Physical examination showed a well-developed, lean girl of 4 years. There was generalized glandular enlargement with the cervical, axillary, inguinal, popliteal, epitrochlear, and supraclavicular nodes involved. The temperature was 100.2° F., pulse 130, and respirations 33.

The abdomen showed a visible bulge confined to the region above the navel. The mass was 9 by 13 cm., fixed, firm, did not fluctuate or pulsate, and appeared to be symmetrical in the midline, not attached to the abdominal wall. It was slightly tender and was mobile with respiration. The rest of the abdomen was flat. The liver and spleen were fully two fingerbreadths below the costal margin. The kidneys were not felt.

Percussion revealed tympany on the left and dullness on the right but on the second hospital day this phenomenon seemed to have disappeared.

The laboratory data showed hemoglobin 44 per cent, red blood cells 2.54 million white blood cells 11,000, polymorphonuclears 63 per cent, eosinophiles 2 per cent, lymphocytes 24 per cent, mononuclears 10 per cent, immature cell 1 per cent. Repeated urine examination was negative. The blood Wassermann test was negative. The tuberculin 1:10,000 was negative. The blood smear showed a marked normocytic, normochromic anemia with variation in size and considerable regeneration, including a number of normoblasts. There was a shift to the left with moderate toxic changes and an occasional myelocyte. The platelets were reduced to about one-half normal, and there were a large number of atypical monocytes. The hematologist's impression read, "This is not a blood dyscrasia but apparently is a reaction to some rather severe condition, and inasmuch as there is enlargement of the spleen here, the things to think about along this line are malignancy, tuberculosis involving the spleen, Hodgkin's disease, although the platelet count is against this latter, and such other malignant conditions."

Roentgenogram of chest showed no pneumonia, tuberculosis, or other definite pathologic change. Abdominal film showed definite moderate enlargement of the liver which displaced the gas-filled colon downward at the hepatic flexure. The spleen and kidneys were not outlined and diaphragm was not unusual in position. Intravenous pyelograms showed satisfactory filling and function of the right kidney and right ureter and bladder filled with diodrast. The left kidney failed to concentrate diodrast and the conclusion was left kidney or adrenal tumor, probably Wilms' tumor. Deep roentgen therapy with dose of 200r was given anteriorly over the left kidney on Dec. 27, 1944.

Whole blood transfusion was given.

Of various clinical impressions, including Wilms' tumor of the left kidney, adrenal neuroblastoma, Hodgkin's disease, and lymphosarcoma, the physician most closely associated with the study of the case favored lymphosarcoma.

NECROPSY REPORT

The patient died Dec. 28, 1944, and necropsy was performed three hours and ten minutes after death. There was marked muscular atrophy and slight rigor mortis was present throughout. The eyes showed slight exophthalmos and sclerae had a slight yellowish tinge, the corneas were clear, pupils equal and regular in outline. The nose showed a small amount of hemorrhagic discharge from both nostrils. The mouth showed parched lips, and normal temporary teeth with purplish discoloration along the gingival margins. There was a large ecchymosis in the labial gingiva inferior to the lower incisors. The palatine tonsils were moderately hypertrophied and slightly hyperemic. The pharynx was moderately injected. The superficial and deep cervical nodes were enlarged, firm, and discrete. The thyroid gland, trachea, and cervical blood vessels were negative. The abdomen was level with the inferior costal margin, with a slight bulge in the upper left quadrant. A small, brownish-red, macular rash was scattered over the abdomen. The external genitalia were normal for a 4-year-old girl. The extremities showed no relevant lesions.

On section of the thorax, the thymus was normal in size and consistency. The left pleural cavity contained about 50 c.c. of hemorrhagic fluid, the right 35 c.c. of similar fluid. The esophagus was negative and the heart normal. The ascending aorta showed a few atheromatous plaques near the coronary arteries. The plaques were bright yellow in color. The lungs appeared normal with no macroscopic metastases found.

On opening the abdomen, the peritoneal cavity contained about 180 c.c. of hemorrhagic fluid. The mesentery showed numerous large ecchymoses, especially near the reflection over the transverse colon.

The liver extended 8 cm. below the inferior costal margin in the midline. There was a large mass in the region of the left kidney which extended from the right border of the spinal column to the left lateral abdominal wall. It was firm in consistency and irregular in outline. There were numerous adhesions between the fundus of the gall bladder and the adjacent serosal surfaces.

A large blood clot was found in the true pelvis. The serosal surfaces were smooth, moist, and glistening. The intestines showed no special lesions. The stomach showed a few small, petechial hemorrhages but the mucosa otherwise appeared normal. The gall bladder and bile ducts were normal. The venae cavae appeared normal.

The liver was normal in size and shape, firm in consistency, brownish red in color, mottled with sharply defined, pale yellow areas varying in size from 1 to 5 mm. in diameter. Sections showed the same type of mottling. The normal structure of the liver was easily discernible.

The spleen showed a few fibrous adhesions.

The pancreas was involved in the tumor mass from which it was dissected out only with difficulty.

The abdominal aorta was not remarkable.

The right adrenal gland appeared normal.

The right kidney measured 7.5 by 4.5 cm. and was firm in consistency. The capsule stripped with ease, revealing a pale, smooth, brownish yellow surface with a few large, punctate hemorrhages from 1 to 3 mm. in diameter. The cortex was normal in thickness and cortical markings were indistinct. The medulla and pelvis were normal. The ureter was normal.

The large mass on the left side arose from the left adrenal.

The left kidney measured 10 by 5.5 cm., was firm in consistency, and the capsule stripped with ease and revealed a pale, uniformly smooth, brownish yellow surface with a few punctate hemorrhages. The cortex was normal in thickness and cortical markings were indistinct. The configuration of the medullary pyramids was completely obliterated by a large, firm, brownish mass which almost completely flattened the pelvis and extended outward in finger-

like projections into the cortex. The corticomedullary junctions were irregular in configuration.

The mesenteric lymph nodes were markedly enlarged and matted together with the mass. Some were firm in consistency, while others were soft and appeared fluctuant. Sections showed white surfaces with irregular dark areas. Some of these hemorrhagic areas were small while others were the size of the entire lymph node. The fluctuant nodes had necrotic centers. The large mass in the region of the left adrenal was 10 by 7 by 6 cm. It was lobulated, irregular in contour, and some of the lobules were soft and fluctuant while others were firm. The mass was divided into lobules by fibrous tissue septa. The cut surface showed small, irregular, white areas within the dark red areas and many of the lobules had necrotic centers.

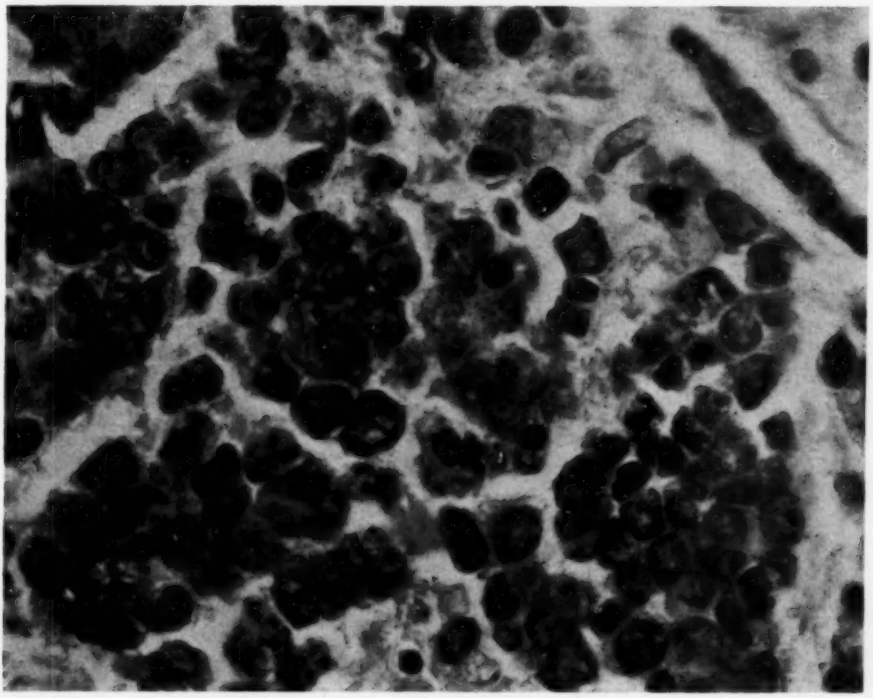

Fig. 1.—Dysgerminoma ovarii. Hematoxylin and eosin stain (×800).

The spleen weighed 30 grams and was macroscopically normal.

The pancreas appeared pale and brownish yellow, with dark red markings in the interlobular septa. Sections showed a pale, brownish yellow surface with a light brown mass extending into the body in fingerlike projections.

The pelvic organs were removed en masse.

The bladder was normal and contained a small amount of straw-colored urine.

The vagina, uterus, and tubes appeared normal for a 4-year-old girl.

The right ovary measured 5 by 3 by 3 cm. The left ovary measured 4 by 2.5 by 3 cm. The external surfaces were purplish red and mottled, with sharply defined yellow areas of varying sizes. On the superior aspect of the left ovary there was a small cavity with necrotic borders. Sections showed a dark red surface with numerous sharply defined, brownish yellow areas

varying in size from 3 to 5 mm. in diameter. These nodules were firm in consistency and comprised the greater part of both ovaries. The blood clot found in the true pelvis appeared to originate from the ruptured left ovary.

Microscopic examination of the lungs disclosed tumor cells in the large vessels. The urinary bladder showed tumor cells in the serosa. The right adrenal showed nests of tumor cells in both the cortex and medulla. The left adrenal was completely replaced by the tumor, which contained prominent areas of necrosis and hemorrhage. The right kidney showed nothing unusual. The left kidney showed very extensive replacement by tumor tissue, with infiltration most marked in the medulla. Some of the glomerular tufts were invaded and almost replaced by tumor sheets, and tumor cells were also seen within many blood vessels. The pancreas showed patchy invasion by nests of tumor cells and a moderate amount of interstitial fibrosis. Lymph nodes had extensive tumor infiltration with prominent areas of necrosis and hemorrhage. In the pulp of the spleen, tumor cells were seen. Nodules of tumor metastases were found in the liver, some small and others confluent, and individual tumor cells were seen in the sinusoids. The ribs and sternum had tumor metastases in the bone marrow.

In the ovaries, the tumor cells had scanty, granular, and slightly acidophilic cytoplasms which surrounded large rounded or oval nuclei, each about 10 to 14 microns in the longest diameter. The nuclei were hyperchromatic with their chromatin material in coarse clumps. Mitotic figures were numerous. The growth was rich in blood supply and hemorrhage and necrosis were irregularly scattered throughout the tumor and the larger metastases. The slides were submitted to Dr. Emil Novak, Chairman of the Ovarian Tumor Registry, who confirmed the diagnosis of dysgerminoma of the ovary.

DISCUSSION

All recent publications on the histopathology of ovarian tumors agree on the description of the structure of dysgerminoma.[6, 8, 9, 11] Novak,[8] in particular, gave an excellent description. Seegar[11] described the tissue microscopically as suggesting the appearance of caviar. However, we have to bear in mind that this applies to the areas in which necrosis, hemorrhage, and other degenerative changes are not found.

It is interesting to note that both Chevassu[2] in 1906 and Chenot[1] in 1911 gave an excellent histologic account of the tumor.

Chevassu[2] in his section on anatomic pathology described "seminome" as a tumor whose cells are rounded and have voluminous ovoid nuclei and whose cytoplasm is markedly reduced. The nucleus is about 12 microns in its longest diameter and contains one, two, or three bright nucleoli. Around the nucleus there is a halo of clear cytoplasm. Peripheral to this halo the cytoplasm takes a deeper stain. He also stated that the cells are very delicate and alter very rapidly and for this reason he recommended very early fixation in Zenker's fluid. He went further to state that a similar picture is met with only in some ovarian tumors.

Chenot[1] in his thesis on "Epitheliomas Primitifs de l'Ovaire" with the assistance of his friend Masson on the histologic technique, arrived at a similar description as that of Chevassu.[2]

With regard to the histogenesis of the tumor, Chenot agreed with Chevassu that both "seminome" and dysgerminoma originated from the sex cell on condition that the sex cell be of "the indifferent type," that is, the sex cell before it differentiates into male or female sex cell. Furthermore, this definition was

written before the application of the hormone tests in the differential diagnosis of ovarian and testicular tumors was common knowledge. Moreover, Chevassu[3] in 1910, in his report on the prognosis of testicular tumors, showed statistically that this tumor gave a better prognosis following surgery than the other testicular tumors.

SUMMARY

In summary, we have reported a case of bilateral dysgerminoma in a 4-year-old Negro girl with rupture of the left ovary resulting in hemoperitoneum, with metastases into the following organs in the order of extent:

1. Left adrenal and left kidney.
2. Lymph nodes, (a) mesenteric (b) periaortic (c) cervical.
3. Pancreas.
4. Liver.
5. Right adrenal.
6. Serosa of urinary bladder and stomach.
7. Bone marrow of sternum and rib.

Vascular dissemination was observed in the following: (a) lungs, (b) left kidney, (c) liver, (d) spleen, (e) peripheral blood.

There was extreme emaciation and mild jaundice.

The early literature on the histogenesis of dysgerminoma and the various case reports found in young patients have been reviewed and presented.

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PHENYLPYRUVIC OLIGOPHRENIA IN A JEWISH CHILD

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IN 1934 Fölling[1] described mental deficiency associated with phenylpyruvic acid in the urine, and so made another inroad into the large group of "primary" mental defectives. Since that time Jervis[2] has reported more than 200 cases of this disease. In contrast to the Tay-Sachs form of idiocy, not a single case was found in a Jewish person. There is a similarity between Tay-Sachs disease and phenylpyruvic oligophrenia in that both are associated with metabolic disorders, the former with a biochemical error involving lipids and the latter involving an amino acid. It is to be noted that a large proportion of Jervis' cases came from mental institutions draining large areas of Jewish population.

The cases to be presented here have the genetic distinction of being the first such cases reported in Jews.

CASE REPORT

A. C. is a 6-year-old white boy, the first-born, whose parents at the time of his birth were 29 years old. The mother's pregnancy was normal and full-term, and labor was uneventful. The infant was bottle fed. Cereals were added at 3 months of age, and vegetables, fruits, eggs, meats, etc., were added in the succeeding months. Ten drops of oleum percomorphum and orange juice in adequate quantities were begun at one month and continued until the present time. At the age of 2 weeks he was operated on for a strangulated inguinal hernia and made an uneventful recovery. His other illnesses included bilateral otitis media at one year and a respiratory infection with high fever at 3 years of age.

The mother noted that the infant's mental development was slow from early infancy. Although he walked at 19 months of age, he didn't say a word until he was 3 years old. He developed some bowel control at one year of age, but had frequent lapses. He developed daytime control of his bladder at 4½ years of age but still wet his bed at night. He never adjusted himself to other children, nor cooperated with them. He still appears afraid of them and always fights with them. He was admitted to one school at the age of 5½ years, but was so difficult to manage that his mother was requested to remove him. He was then placed in another school, where he was retained by means of rewards and punishment until he began to vomit. The vomiting gradually became worse and he was admitted to the Beth Israel Hospital as a possible surgical case. No organic cause for this vomiting was found, and it subsided without any specific therapy.

When the acute episode subsided, the following positive findings were noted: (1) a slim, dull-looking boy with fair complexion, blue eyes, and light brown

From the Pediatric Service of Dr. Philip Cohen, Beth Israel Hospital.

hair; (2) head circumference only 18 inches (2½ inches less than normal); (3) auricles abnormally shaped; (4) right inguinal scar and atrophic right testicle.

The neurological examination revealed the following positive findings: (1) hyperactive deep reflexes; (2) halting type of gait; (3) diminution of associated hand swinging when walking; (4) hypotonia; (5) generalized muscular weakness.

Mentally he was a hyperactive, noisy, unkempt child. His speech was indistinct, his vocabulary was very limited. He showed little interest in the other children on the ward other than to beg for candy or toys. He was frequently incontinent of both urine and feces. On one occasion he was noted tasting his own stool; on another he was seen eating paper.

The positive laboratory findings were: (1) urine was persistently positive for phenylpyruvic acid; (2) the electroencephalogram showed slow waves of high voltage but no noticeable focal abnormalities; (3) the psychometrics showed an I.Q. of 34 on (a) the revised Stanford Benet, (b) the Cornell Coxe Performance Scale, and (c) the Goodenough Drawing Test.

The family history is contributory. The father showed phenylpyruvic acid in the two specimens of urine tested. His I.Q. as measured on the Bellevue-Wechsler test was found to be 69. He is a presser of gloves, works steadily, and earns about $35.00 per week.

He is aware of his son's mental retardation, has expressed interest, and shown cooperation in the various tests done on the child.

The mother, as well as the younger sibling of this marriage, have a normal mentality and no phenylpyruvic acid in the urine. The parents are not blood relations, both born in different towns in Russia. They state that their geneology shows all their ancestors have been Jews.

Penrose,[4] and particularly Jervis,[3] have presented careful and detailed studies on the genetics of this disease. The latter has postulated that it is transmitted by a rare recessive autosomal gene present in both parents who are heterozygous. The theoretical expectation in a marriage involving two heterozygotes is that 75 per cent of the siblings will be normal, and 25 per cent affected. In an analysis of 200 cases of phenylpyruvic oligophrenia, Jervis found that 42 per cent of the offspring of carriers of this disease were affected. However, correction of the raw percentage by special methods of statistical analysis reduced the figure to 25 per cent. These findings, therefore, seemed to confirm Jervis' theory of the inheritance of this disease. Consanguinity is an important factor in the incidence of this disease, which is more common in Norway than in England, more common in England than in the United States.

Jervis reported one instance where the mating of an affected individual with a normal individual resulted in four siblings, two affected and two normal. He put forward the hypothesis that the unaffected parent was heterozygous. He pointed out that although this was unlikely in the absence of consanguinity, it was not impossible when one considered that the percentage of heterozygotes or carriers was above 1 per cent.

The case presented in this paper is very similar genetically to the one just quoted from Jervis. Again one out of two siblings are affected and one must

postulate that the mother is a heterozygote if the method of inheritance is by a single autosomal recessive gene. However, the presence of two such cases cast some doubt as to the validity of this theory of inheritance in this disease.

Although the gene for phenylpyruvic oligophrenia is a recessive one, it is noted that the carriers, the heterozygotes, are predisposed to mental deterioration. It is, therefore, believed that the gene for phenylketonuria is not completely recessive. Inasmuch as carriers of the recessive gene are about 1 per cent of the population and the actual incidence of the disease is about 1:25,000, it is possible that many of the mentally ill are carriers of this gene.

It seems to us that the father of our patient was actually a forme fruste of phenylpyruvic oligophrenia. He showed phenylpyruvic acid in his urine and scored 69 on the Wechsler-Bellevue test. His neurological examination was within normal limits. Despite his borderline intelligence, he made a satisfactory and independent economic and social adjustment in a strongly competitive community such as New York City. Jervis reported two patients with this disease with psychometrics of 60, but neither showed as good a social adjustment as the patient just reported. It is not unlikely that further investigation will reveal other unsuspected "forme fruste" cases of phenylpyruvic oligophrenia.

The metabolic error in this disease is explained in the following way. Phenylalanine is converted to phenyllactic acid and phenylpyruvic acid or directly to tyrosine. The phenylpyruvic acid is then converted to tyrosine. In this disease the enzymes necessary for these conversions are deficient. Jervis and associates found that the blood of patients with phenylpyruvic oligophrenia contained unusually large amounts of phenylalanine but no phenylpyruvic acid nor phenyllactic acid, even after the latter two substances were administered. They concluded that the kidneys were able to deaminate phenylalanine although the extra renal tissues were unable to oxidize it. Penrose and Quastel found that the administration of alanine and tyrosine to phenylketonurics caused no change in the excretion of phenylpyruvic acid, whereas the ingestion of dl-phenylalanine, L-phenylalanine and d-phenylalanine led to an increased excretion of phenylpyruvic acid.[10]

Levine and collaborators[8] found that premature infants, when given high protein, as cow's milk, excrete in the urine excessive amounts of p-hydroxyphenylpyruvic and p-hydroxyphenyllactic acids. This disorder of premature infants was prevented by administration of ascorbic acid. It was possible to induce a similar condition in full-term infants by giving large amounts of phenylalanine or tyrosine and abolishing it again with extra ascorbic acid. Closs and Fölling[9] found small amounts of phenylpyruvic acid in the urine of rats with vitamin B_1 deficiency. They concluded that thiamine was implicated in the oxidation of phenylpyruvic acid.

Phenylpyruvic acid is never found in the urine of normal people, whereas phenylketonurics excrete from 0.5 to 3 Gm. daily.

Jervis tried to determine whether phenylpyruvic acid was toxic and interfered with growth and development. He, therefore, gave large quantities to one litter of kittens and used another litter as a control. No difference was noted in the two litters. On the other hand, no proof was found that the mental defect was the cause of the metabolic error.

Diagnostic Features.—The two cardinal features in the diagnosis of this disease are mental retardation, almost invariably of a severe grade, and the presence of phenylpyruvic acid in the urine. Other neurological findings commonly present are not diagnostic. The most prominent of these are muscular rigidity, alterations of posture and gait, tremors, and athetoid movements. It is also to be noted that these children are characteristically fair in complexion and not unattractive in appearance despite their low intelligence. Approximately, one-half of the cases reported showed skin lesions eczematous in nature.

Therapeusis.—Replacement therapy by the administration of phenylalanine or tyrosine has proved futile, for there is a deficiency of an oxidizing enzyme for the proper metabolism of phenylalanine or its deaminated derivatives, with failure of normal conversion to tyrosine. Administration of large doses of Vitamin C is similarly futile, as its oxidation action is on p-hydroxphenylpyruvic acid, which is a deaminated derivative of tyrosine. Since in this form of idiocy there is a failure of conversion to tyrosine, ascorbic acid is useless as an oxidizing agent for phenylpyruvic acid. Attempts are now being made to test the efficacy of glutamic acid in this disease; this is a nonspecific method of approach, for this acid has been of value in increasing the metabolism of brain cells and raising the intelligence in other mental defective conditions.

SUMMARY

A case of mental deficiency with phenylpyruvic acid in the urine is reported in a Jewish child for the first time. Other neurological and psychiatric features were present. The father of this child presents a forme fruste of the disease. The genetics and metabolic error of this disease are briefly discussed.

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AN OXYGEN-HUMIDITY-AEROSOL UNIT FOR INFANTS

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FOR many years the croup tent and steam kettle have been of recognized value in the treatment of laryngotracheobronchitis. More recently "cold steam" methods have removed the disadvantages of high temperature humidity. Such a method was developed in the Children's Hospital of Pittsburgh by Simpson,[1] utilizing a water sprayer or oxygen humidifier resembling the nozzle on a garden hose with a jet of oxygen to further break up the water droplets. This equipment has proved satisfactory over a period of four years and has been recently modified by the addition of an aerosol nebulizer, in order to broaden its clinical application. While the addition of aerosols to oxygen tents is not new[2] the modification described in this paper results in a compact unit with a wider range of usefulness than existing models.

Apparatus.—An additional iron strap is welded to the back of a standard open top infant oxygen tent frame, one inch above the bottom (Fig. 1). A plate of acrylic plastic (Plexiglass) measuring 19 x 17¾ x ¼ inches, is attached to the back of the frame by bolts. Two round openings, lined with ¼ inch sponge rubber sleeves, are seen in the plate 7½ inches below the top and 2½ inches from the midline, which hold snugly in position a standard glass aerosol vaporizer and the metal oxygen-humidifier.[1] The whole is covered with a standard clear plastic canopy designed for the frame, in which two apertures were made to admit the long arm of the nebulizer and the nozzle of the oxygen-humidifier. Oxygen is delivered to these through a flow meter and a Y-shaped metal connecting piece with stop valves on each arm. In this way oxygen can be directed into either outlet independently. Water is provided for the humidifier from any reservoir placed at the same level or above the spray nozzle, such as a 1,000 c.c. glass intravenous bottle on a stand. The assembled equipment* is seen in Fig. 2.

Operation.—The infant is first clothed in a waterproof cap and jacket and placed in the tent through the sleevelike opening in the front of the canopy, with his head on a waterproof pillow. When using the oxygen-humidifier, the top of the canopy is left open over the rear third to aid in cooling the tent. Oxygen is run through the humidifier at 6 L. per minute and the droplet size of the spray is adjusted by the needle valve. By screwing in the needle valve a very fine mist can be introduced into the tent so that a humidity of 80 to 90 per cent can be achieved within one-half hour. The tent temperature then

From the Children's Hospital of Pittsburgh and the University of Pittsburgh School of Medicine.

*Obtained from Medicinal Oxygen Co., 3939 Butler St., Pittsburgh 1, Pa.

ranges from 70 to 79° F., the latter temperature being reached with a room temperature of 90° F. and oxygen content varies from 41 to 46 vols. per cent.[3] Water consumption by the unit amounts to 100 to 200 c.c. per hour and the attendant nurse must sponge out the accumulated water from time to time.

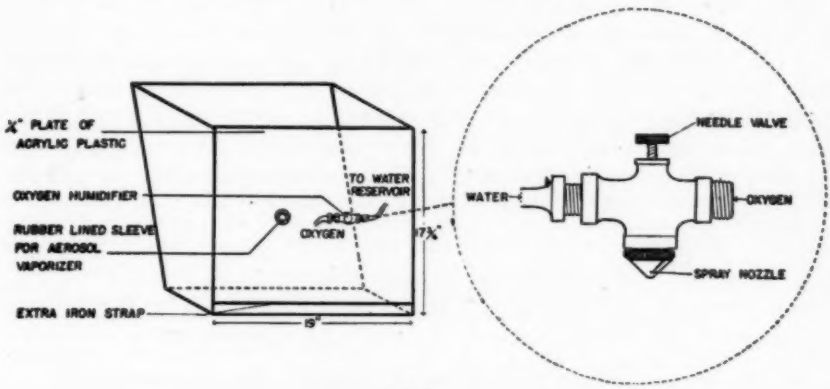

Fig. 1.

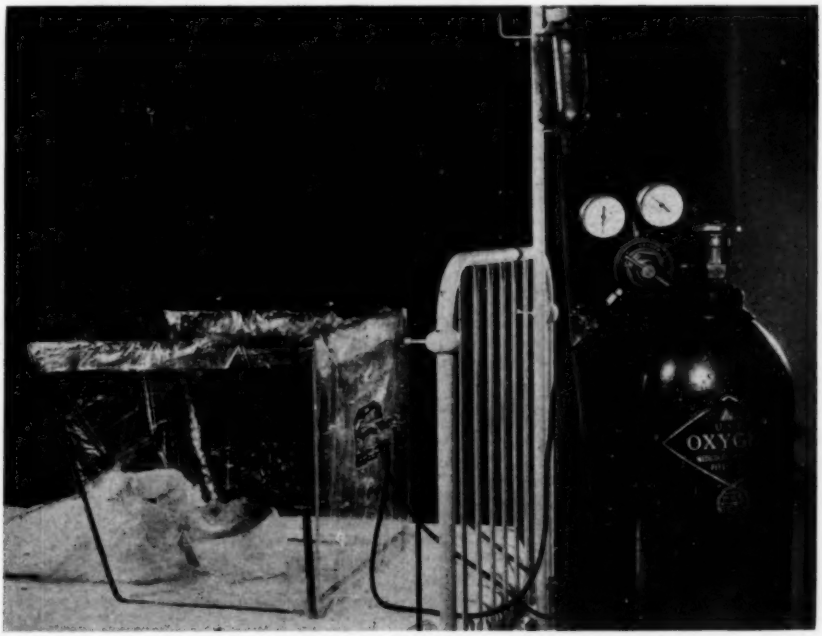

Fig. 2.

Aerosol penicillin is administered every three hours in concentrations of 75,000 to 100,000 O.U. in 3 c.c. of normal saline, after redirecting the oxygen flow from the humidifier to the vaporizer. This antibiotic reaches the patient effectively as can be seen in Table I, where serum penicillin assays[4] were made after all the penicillin had been nebulized. During the administration of the aerosol, the top of the canopy is kept closed to reduce diffusion and the humidifier is cut off as the large droplets would probably precipitate the aerosol.

This equipment has been used prinicipally for laryngotracheobronchitis cases but also is of use in conditions requiring aerosol antibiotics alone, such as cystic fibrosis of the pancreas. The children are contented in a tent where they can see all around, while the nurses can watch them with ease. The relatively high oxygen content is felt to be advantageous in dyspnea and the ease of administration of penicillin or streptomycin does away with the spasm associated with intramuscular injections.

TABLE I. LEVELS OF PENICILLIN IN SERUM AFTER AEROSOL PENICILLIN

PATIENT	AGE (MO.)	WEIGHT (LBS.-OZS.)	TIME* (MINUTES)	PENICILLIN (OXFORD UNITS) DOSE IN 3 C.C. ISOTONIC SALINE	PENICILLIN (OXFORD UNITS) BLOOD LEVEL PER C.C. SERUM
C. M.	2	5 – 1	21	75,000	0.125
E. S.	3	7 – 12	21	75,000	0.062
J. W.	5	10 – 14	21	75,000	0.062
J. W.	5	10 – 9	18	100,000	0.250
J. W.	5½	10 – 13	20	75,000	0.125
M. Y.	8½	15 – 12	20	75,000	0.250
M. Y.	8½	15 – 2	30	75,000	0.250
W. J.	12	15 – 3	22	100,000	0.250
			195		0.000
M. F.	14	19 – 1	21	100,000	0.500
			170		0.000
A. McG.	15	23 – 0	20	100,000	1.000

*Time from start of penicillin.

SUMMARY

A new type of equipment is described which provides oxygen, humidity, and aerosol antibiotics for infants. It is possible to produce appreciable levels of serum penicillin and the relatively high oxygen content with a high humidity is felt to be valuable.

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Case Reports

TOXICITY OF CARONAMIDE

Report of a Case

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THE use of Caronamide (4′-carboxyphenylmethanesulfonanilide) for the enhancement of penicillin blood levels has been advocated by several authors.[1, 2, 3, 4] They mentioned no toxic effects of Caronamide. Crossen[3] found no evidence of systemic toxicity in his series of cases, but stated that, as with any new compound, some type of sensitivity or toxic manifestation is likely to occur. Meads and associates[5] stated that mild toxic reactions were observed when Caronamide serum level exceeded 40 mg. per cent. Rapaport,[6] in a clinical evaluation of Caronamide in children, found no manifestations of toxicity that necessitated withdrawal of the drug. He reported rashes in three of the twelve patients, which apparently faded even while administration of the drug continued.

The following case of a patient with subacute bacterial endocarditis successfully treated with penicillin and Caronamide illustrates the toxic manifestations of fever, increased bleeding time, and increase in capillary fragility* presumably caused by Caronamide.

REPORT OF A CASE

E. R., an 11-year-old white girl, was admitted to Strong Memorial Hospital because of chills and fever existing for five days. For the previous two months the patient had: (1) a hacking cough and nasal discharge; (2) dyspnea on exertion; and (3) a weight loss of five pounds; although (4) she had experienced no joint or abdominal pains, nose bleeds, or urinary symptoms. Her past history revealed that she had cardiac enlargement and a murmur since the age of 10 months but without symptoms or disability. Her local physician reported no change in the long-standing heart murmur.

Physical Examination.—Temperature was 38.5° C.; pulse, 110; respirations, 20; blood pressure, 105/75. She was a well-developed and well-nourished girl 11 years of age, appearing moderately acutely ill. She was emotional and hypersensitive but quite cooperative. There was moderate injection of the nasal mucous membranes. Cardiac examination revealed enlargement to the left, a systolic thrill maximum at the pulmonic area, and a systolic murmur heard over the entire precordium. No diastolic component was present. Pulsations were felt in dorsalis pedis arteries. There was no cyanoses or clubbing of fingers. No petechiae were found.

Laboratory Findings.—Red blood corpuscles were 5.4 million; hemoglobin, 13 Gm.; white blood corpuscles, 12,700. Differential polymorphonuclears, 83

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*The capillary fragility was measured by means of an instrument consisting of a glass suction cup constructed to cover one centimeter of area and connected by rubber tubing to a mercury manometer. Negative pressure was obtained with a well-greased 50 c.c. syringe attached to the manometer. Negative pressure of 20 mm. of mercury for one minute on the extensor surface of the forearm of a normal child will show from 0 to 5 petechiae. In testing, a child of comparable age and sex to the patient was used as a control. We have found this method superior to the standard tourniquet test because the same general skin area may be repeatedly used and the limited area of one centimeter makes counting the petechiae obtained relatively easy.

per cent; lymphocytes, 16 per cent; monocytes, 1 per cent; normal appearing red cells with adequate platelets. Urine normal. Throat culture: *Staphylococcus albus* and *Streptococcus viridans*. Blood culture: Positive for *Str. viridans* on first, third, fourth, and eighth hospital days; six subsequent blood cultures were sterile. X-ray and fluoroscopic findings revealed general cardiac enlargement with no specific diagnostic findings. Electrocardiogram indicated a right axis deviation and auricular enlargement.

A diagnosis of subacute bacterial endocarditis caused by *Str. viridans*, superimposed on a congenital heart lesion, was made on her sixth hospital day. It was felt that she did not have a patent ductus arteriosus. Specific therapy was given as follows: 50,000 units of penicillin every three hours for the first day, increased the following day to 200,000 units every three hours plus Caronamide 2.0 Gm. every four hours. Twenty-four hours after institution of therapy her fever had subsided. Penicillin blood level taken on the eighth hospital day was 2.56 units per cubic centimeter just before penicillin administration, and 5.12 units per cubic centimeter forty-five minutes after the drug was given. On her fourteenth hospital day, penicillin dosage was reduced to 200,000 units every six hours in view of the high blood level of penicillin. The patient had no temperature elevation above 38° C. from her seventh to her sixteenth day. She gradually improved both symptomatically and clinically.

On her seventeenth hospital day the patient's temperature rose to 38.2° C. and on the nineteenth and twentieth days reached 39° C. and 38.6° C., respectively. On the twentieth day petechiae were observed when a tourniquet was applied for the withdrawal of blood for culture. Studies revealed that (1) bleeding time and petechial count were increased; (2) prothrombin time, clotting time, and platelet count were normal; (3) blood cultures taken at this time were sterile. Caronamide was discontinued and penicillin dosage interval was shortened to every three hours. Within six days the petechial count dropped from nineteen to six.

On the twenty-sixth day, test doses of Caronamide were given—two doses, 2 Gm. each at a four-hour interval. At midnight the patient complained of nausea, vomiting, and inability to sleep. Her temperature rose to 39.5° C., and a scarlitina-form rash of mild intensity was noted on her neck and chest. Twelve hours after the Caronamide, bleeding time and petechial count were increased. Urine examination revealed the presence of a reducing substance. This substance was identified as a mixture of fructose and a disaccharide. All symptoms subsided within twenty-four hours.

From the twenty-eighth until the forty-ninth day the patient's course was essentially uneventful. Blood cultures were sterile on the thirty-fourth and forty-first days. Penicillin therapy was stopped on the fortieth day, after thirty-five days of treatment and a total of forty-four million units.

In order to rule out a high penicillin level as an etiologic factor in the previously mentioned findings, nine days after the end of penicillin therapy two 2 Gm. doses of Caronamide were again given at a four-hour interval. Three hours after the second dose the patient complained of headache and general malaise, and in three hours more her temperature rose to 38.5° C. There was a marked increase in petechial count at this time, and a reducing substance identified as fructose and pentose was found in the urine. No significant alteration of bleeding time was noted during this episode. She was asymptomatic and afebrile twenty-four hours later.

Four days later the patient was started on 60 mg. Rutin every four hours in preparation for a repeat test with Caronamide, as before two 2 Gm. doses at a four-hour interval. There were no significant changes in the patient's condition either symptomatically or clinically with this test. The petechial count was elevated one day only, bleeding time and temperature were normal,

and no reducing substance was found in the urine. The patient was discharged clinically well fifty-eight days after admission.

DISCUSSION

In Fig. 1 is illustrated the condensation of the therapeutic chart. The temperature curve represents the highest daily temperature recorded.

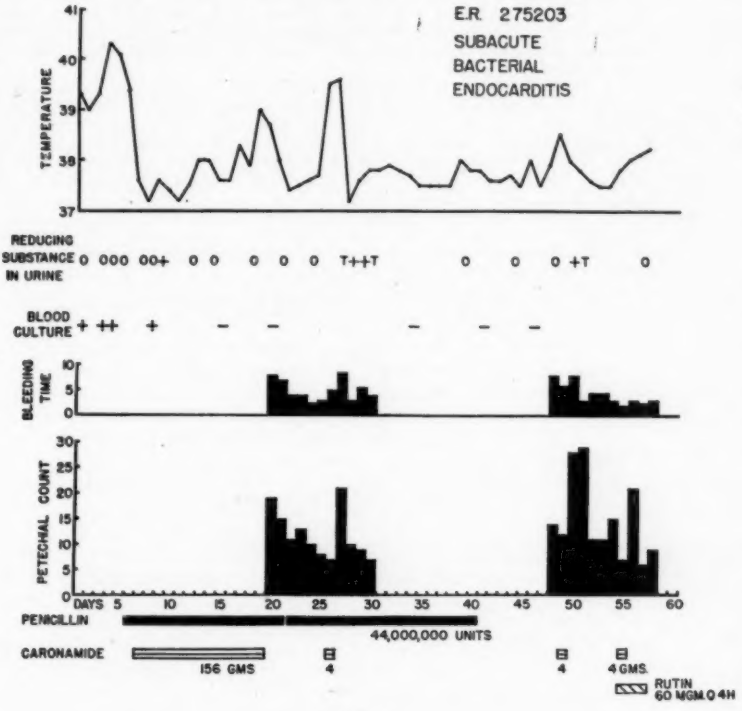

Fig. 1.

Although the symptoms and signs shown by this patient did not constitute serious toxic reactions, they did serve to confuse the picture of the patient's progress. The toxicology behind the Caronamide reaction as manifested by this patient is not clear. Rutin apparently had some beneficial effect in preventing capillary fragility and increase in bleeding time. Beyer and his associates[7] have studied extensively the pharmacology and toxicology of Caronamide, but did not experience reactions such as illustrated by our patient. It is felt that until more clinical and laboratory experience has been obtained, Caronamide should be used with caution.

SUMMARY

1. A case of subacute bacterial endocarditis in an 11-year-old girl was successfully treated with penicillin and Caronamide.

2. A reproducable reaction consisting of fever, increased capillary fragility, and increased bleeding time occurred, presumably as a toxic effect of the Caronamide.

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PULMONARY GANGRENE IN A CHILD FOLLOWING ASPIRATION OF TIMOTHY GRASS

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A VARIETY of vegetable foreign body that is commonly aspirated into the tracheobronchial tree is timothy grass *(Phleum pratense)*. It is of interest because of the severity of the complications that may follow prolonged retention and because of the actions peculiar to this foreign body.

The most common complications of long-retained matter are lung abscess, suppuration, bronchiectasis, and, rarely, gangrene. The following case is presented because of the presence of the latter sequela.

CASE REPORT

The patient, a white female infant aged 21 months, was admitted on Aug. 27, 1941, during an illness of twenty-three days' duration. At the onset she had swallowed some timothy hay and on the day following this began to cough up two to three ounces of foul-smelling sputum several times a day. Vomiting accompanied the cough, which became progressively worse. The latter persisted for four weeks, at which time the child began to whoop and assume the clinical picture of pertussis. A week prior to admission progressive dyspnea developed along with the symptom of pain and oppression beneath the sternum. There was severe anorexia and considerable weight loss.

Birth and development had been normal. The child had had exanthem subitum in April, 1941, followed by what the mother described as pneumonia for three days, although this could not be substantiated. There was no significant family history.

Examination on admission showed a well-developed but undernourished, somewhat emaciated, pale child weighing 19 pounds. Temperature was 101.4° F., pulse 120 per minute, respiration 50 per minute and labored. The skin and mucous membranes showed marked pallor. The breath had a foul odor. The tonsils were moderately enlarged and the pharynx showed an accumulation of mucopurulent material. Examination of the chest revealed markedly decreased breath sounds, marked dullness in the lower half of the right lung with many coarse, moist râles throughout this lung after coughing. The examination of the left lung showed hyperresonance with emphysematous sounds throughout. The heart was normal and not displaced. The spleen was enlarged 2 cm. below the left costal margin. The remainder of the abdomen was normal. There was clubbing of the fingers. The remainder of the physical examination was negative.

Initial hemogram showed 2.9 million erythrocytes with 6.5 Gm. of hemoglobin, 30,250 leucocytes with a predominance of polymorphonuclear cells. Urinalysis was normal. Roentgenogram revealed the heart and left lung to be normal. The right costophrenic angle was obliterated by a homogenous shadow extending to the level of the fifth interspace anteriorly, which had the appearance of fluid. Above this level and involving most of the lungs were homogeneous shadows interspersed with spherical, translucent areas.

Institution of a high caloric diet, fluids, sulfathiazole, and postural drainage allowed for some recovery of purulent, yellow sputum but little clinical improvement. The temperature was elevated irregularly between 100 and 103°

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F. On August 30, bronchoscopic examination revealed the left main bronchus to be clear but slightly inflamed. The right was filled with foul, watery pus. The mucosa of the latter was inflamed and granulation tissue, which bled when touched, was visible. The filtered pus contained granulation tissue and numerous particles thought to be timothy hay. Posterior-anterior, right and left oblique x-ray examinations after bronchoscopy showed multiple abscesses and one large cavity 5.0 cm. in diameter.

On Sept. 3, a resection of a segment of the ninth rib under local anesthesia was performed with removal of several large pieces of necrotic lung tissue from the right pleural cavity. Microscopic examination of the tissue showed chronic inflammation but nothing characteristic of any specific infection. A large drainage tube was inserted into the pleural cavity. Subsequent x-ray showed no fluid level and showed that adequate drainage had been established. A slight right pneumothorax existed.

Postoperatively the child responded poorly. The temperature remained irregularly elevated between 100 and 102° F. The blood picture was improved slightly by transfusion of whole blood. Portable x-ray examination made two days before death showed the large cavity at the right lower lobe. Above the abscess cavity was a dense shadow. The right upper lobe was partially collapsed. Despite all measures the child expired on Sept. 10, 1941, thirty-seven days after the aspiration.

Autopsy findings were significant only in reference to the lungs. The left lung was normal except that pus could be expressed from the bronchioles throughout. The right lung showed only a shell of the lower and middle lobes. The entire lower cavity had been completely drained of necrotic tissue and pus. The upper lobe was made up of a small air-bearing area toward the hilus with the remainder consisting of three, intercommunicating, large cavities filled with dirty, foul-smelling, necrotic tissue and pus. The entire bronchial mucosa revealed a marked reddening and edema but was unobstructed and free of foreign body except at the distal end of the right lower bronchus where a piece of timothy hay 5 mm. in length was found. Considerable fibrosis was noted in the neighboring lung tissue. Microscopic examination of the lungs revealed a thickened pleura with an increase of connective tissue about the bronchi and blood vessels. Some epithelialization of the alveolar walls was evident, the latter being thickened. An infiltration of round and plasma cells and a few polymorphonuclears were seen. The fibrotic lung merged into necrotic tissue with only the connective tissue and a few round cells remaining. The appearance was that of a necrosis or gangrene of the lung.

DISCUSSION

Jackson and Jackson,[1] Clerf,[2] and Seydell[3] have reported cases of aspiration of timothy grass with records of removal by bronchoscopy and the discussion of bronchiectasis, abscess, and the more serious complications of metastatic suppuration and severe hemorrhage. Butler and collaborators[4] were able to effect a cure in two cases of suppurative disease and bronchiectasis by lobectomy. Purcell[5] reported the case of a remarkable sojourn of timothy grass which was aspirated, then propelled by coughing throughout the bronchi to the periphery and eventually out through the chest wall. This case exemplifies the ability of timothy grass to be propelled along and anchored until coughing occurs, when it is moved along head first. Carter and Welch[6] also discussed the peculiarities of this foreign body and summarized eight cases, seven of which patients were benefited by lobectomy.

There are no characteristic bacteriologic patterns or pathologic changes attributed specifically to this foreign body. No previous mention has been made

of gangrene following aspiration and suppurative lung disease, although the sequence of events is not an unusual pattern. This may be due to some confusion between pulmonary abscess and gangrene. Abscess is a suppurative process due to pyogenic organisms, while gangrene is a more severe necrotizing lesion most often due to oral spirochetes, fusiform bacilli. and vibrios (Miller-Vincent organisms). The oral flora of young children does not contain these organisms. This probably explains the fact that there are fewer spirochetal abscesses in children than abscesses due to other organisms. As the oral flora changes from the pyogenic organisms and staphylococcus, the anaerobes are more prominent. Associated with this change are oral lesions, dental caries, and gingivitis.

Roma[7] in 1905 was the first to report the presence of spirochetes and fusiform bacilli in the lung, and he believed that carious teeth were the source. Pulmonary tissue may be invaded by Miller-Vincent's organisms to produce bronchitis, pneumonitis, gangrene, and pleurisy. Pulmonary gangrene is relatively uncommon in children and, like abscess, is most frequently found in the lower lobe. The nature of the cough reflex in young children and the failure to expectorate after coughing with swallowing of infective material, is an important factor in producing lung abscess and subsequent complications. The pathologic process of pulmonary gangrene is one of progressive and extensive molecular necrosis with the formation of cavities.

SUMMARY

1. A case of pulmonary gangrene following aspiration of timothy grass is presented.

2. A discussion of the foreign body and a brief review of the literature is included.

3. The pathologic and bacteriologic pattern is briefly discussed.

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FATAL LEPTOSPIROSIS (WEIL'S DISEASE) IN A NEWBORN INFANT

Case of Intrauterine Fetal Infection With Report of an Autopsy

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LEPTOSPIROSIS or Weil's disease is a specific infection usually caused by the Leptospira icterohaemorrhagiae.[1] This organism commonly infects wild rats, and human infections result from contact with the rat's excreta. Two other strains of Leptospira, *L. canicola* and *L. icterohemoglobinuriae vitulorum* produce a similar disease in dogs and cattle respectively, and both of these organisms have been known to produce Weil's disease in man.[2, 3] This disease is probably more common than generally suspected, since about 40 per cent of the human patients are not icteric, and since there is evidence of latent leptospiral infections in rats, dogs, and human beings.[2] It is believed that the leptospiras usually enter the body through the abraded skin, mucous membranes, or possibly the gastroenteric tract.[1] It has been shown, however, that Leptospira may infect fetal guinea pig tissues after passing through the placenta.[4]

This mode of infection may have occurred in one human patient whose case is recorded in the literature.[5] The purpose of this paper is to report the first proved case of fatal leptospirosis in a newborn infant. The course of the illness, the severity of the pathologic lesions, and the post-partum presence of agglutinins in a high titer in the mother's serum indicated that the infection of the infant was acquired during intrauterine life.

CLINICAL HISTORY

H. S., a 29-year-old nulliparous female, was first seen in the third month of pregnancy. The only significant abnormalities noted on physical examination were severe dental caries, obesity, and thyroid hypertrophy. Her family and past history were noncontributory. Except for measles, chicken pox, and tonsillitis during childhood, she had never been ill. In the post-partum period the patient was questioned further on possible contacts with Leptospira. During the period from 1938 to 1943, she was a waitress in a restaurant infested with rats, but during this period was not ill at any time. She had two pet dogs from 1945 to 1948; these animals had not been ill. There was no other history of contact with animals or exposure to possibly contaminated water. Her husband was a mail carrier; he had had no illnesses and had no contact with animals.

The patient's prenatal course was uneventful except for slight dependent edema during the last two months of pregnancy. This responded to sodium restriction; there was no associated albuminuria on hypertension. Laboratory examination gave normal findings.

After a normal labor of three hours, the patient delivered a male infant weighing 3,450 Gm. on May 18, 1947. The delivery was facilitated by the use of forceps at the outlet and by an episiotomy.

The infant appeared normal at birth with good color and crying. While the skin was not icteric, the vernix caseosa and the amniotic fluid were stained with bile. He was breast fed until two feedings before death. The neonatal course was normal until thirty hours after birth, when moderate icterus appeared. At thirty-eight hours after birth, the infant became listless, icteric, cyanotic, dyspneic, and had several convulsions. The edge of the liver was palpable. The urine was dark, due to the presence of bile. Examination of the

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blood showed: hemoglobin 150 per cent (26.7 Gm. per 100 c.c.); red blood cells, 6.2 million per cubic millimeters; white blood cells, 11,600 per cubic millimeters; differential count, neutrophilic leucocytes 83 per cent, neutrophilic myelocytes 3 per cent, lymphocytes 14 per cent. There were 4 nucleated red blood cells per 100 white blood cells. Spinal puncture showed nothing abnormal. The infant's condition deteriorated rapidly, and death occurred six hours after the onset of the illness, and fourteen hours after the appearance of icterus.

AUTOPSY REPORT

The autopsy was performed ten hours after death. The body measured 52 cm. in length and weighed 4,175 Gm. The skin and scleras were mildly icteric. A small amount of sanguinous, mucoid fluid was present in the nose and mouth. There were no external hemorrhages. The attached umbilical cord was dry and contracted. The pleural and peritoneal cavities contained an increased amount of bile-containing fluid.

The thyroid and thymus glands showed nothing abnormal. The latter weighed 12 grams.

The heart weighed 20 grams, and had an entirely normal appearance except for a 2 mm. epicardial hemorrhage at the base of the pulmonic valve. There was a large amount of sanguinous, frothy fluid in the trachea and bronchi. Both lungs were heavy, and weighed 90 grams together. There were numerous subpleural hemorrhages, and the parenchyma was diffusely congested, edematous, and showed considerable intraalveolar hemorrhage.

The liver was enlarged and weighed 195 grams. There was rounding of the anterior edge. The hepatic parenchyma was firm and dark red in color, but its consistency was normal. There was no capsular wrinkling either before or after fixation. The gall bladder and extrahepatic ducts were explored, and were entirely normal. There was enlargement of the spleen, which weighed 23 grams. It had a firm, dark red, nonhyperplastic pulp. The pancreas was normal.

The adrenal glands were of normal size and weight. Their cut surfaces showed the usual neonatal congestion of the inner cortical layers. Each kidney weighed 15 grams, and neither showed gross pathologic changes.

The rest of the genitourinary tract was normal except for the testes, which showed diffuse hemorrhagic infiltration.

The great vessels, bone marrow, gastroenteric tract, and mesenteric lymph nodes showed nothing abnormal.

The scalp, skull, and intracranial contents were entirely normal grossly. The brain was not icteric.

MICROSCOPIC DESCRIPTION

The heart was normal except for a few small perivascular hemorrhages in the myocardium. There was marked vascular congestion in the lungs, and in addition there was recent extensive hemorrhage in the interstitial tissues and within the alveolar and bronchial spaces. Many alveoli were filled with serous fluid, but there was no inflammatory reaction.

There was extensive destruction of the liver with disruption of the cords of hepatic cells (Fig. 1). There was tremendous dilatation of the sinusoids, which were distended with blood. The portal triads and central veins were still visible. Large numbers of hepatic cells had been destroyed and had disappeared. Most all of those remaining showed degenerative and necrotic changes, including cytoplasmic vacuolization and swelling, and swelling or pyknosis of the nuclei. Many remaining cells were detached from their basement membranes. While all the hepatic cells were involved in the degenerative process, those adjacent to the portal triads were better preserved. Both the triads and sinusoids contained moderately abundant hemopoietic tissue. There was no evidence of stasis of bile either in the small bile ducts or biliary canaliculi. Nowhere was there evidence of regeneration of the hepatic cells.

The splenic lymphoid follicles were normal; the splenic pulp was congested, and contained large numbers of well-differentiated hemopoietic elements. The gall bladder and pancreas showed nothing abnormal. Submucosal hemorrhages were present in sections from several levels of the gastroenteric tract.

There was a normal degree of neonatal capillary congestion and cellular degeneration of the inner cortical layer of the adrenal glands. There was no structural alteration of the renal glomeruli, but glomerular spaces often con-

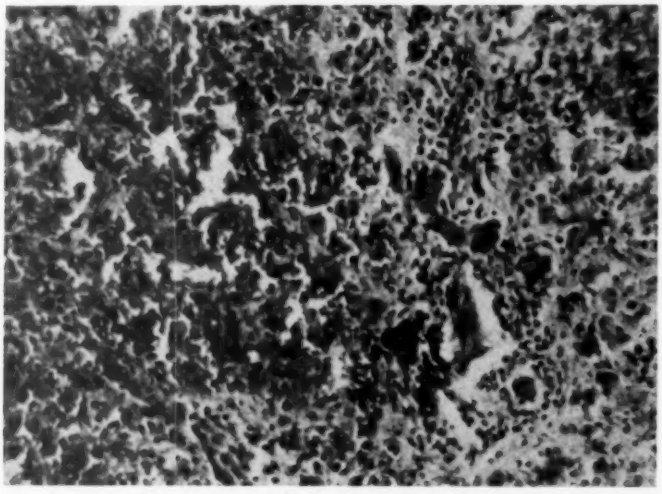

Fig. 1.—Liver showing parenchymal necrosis and sinusoidal engorgement. Hematoxylin and eosin stain (× 210).

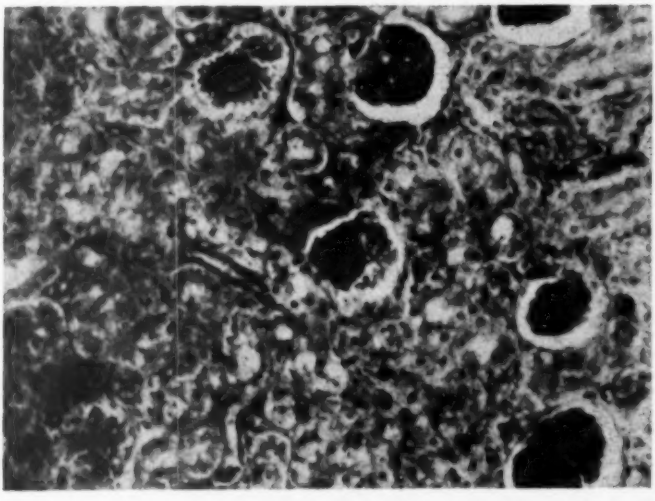

Fig. 2.—Kidney showing tubular degeneration. Hematoxylin and eosin stain (× 210).

tained precipitated protein and desquamated epithelial cells. There were striking degenerative changes in the tubular epithelial cells, particularly of the proximal and distal convoluted groups (Fig. 2). Similar but less marked alterations of the tubules comprising Henle's loops were noted, but the collecting tubules were lined by normal epithelial cells. The damaged tubular cells were markedly swollen, vacuolated, and had abundant eosinophilic cytoplasm. In addition, many had swollen, pale, or pyknotic nuclei. The nuclei were completely absent in some necrotic cells which were desquamating into the tubular lumens. Some tubules contained protein and epithelial cellular casts, and a few were occluded by casts containing bile. There was marked vascular congestion of the entire renal tissue with small perivascular hemorrhages in some areas. While small hemopoietic foci were encountered, there was no renal inflammatory reaction. The renal pelvic tissues, bladder, and prostate gland showed nothing abnormal.

The testicular blood vessels were congested, and there were many perivascular hemorrhages. The aorta was normal.

While there was considerable hemopoietic activity in the mesenteric and pre-aortic lymph nodes, there were no hemorrhages or inflammatory reaction. The thymus gland was normal except for several interstitial hemorrhages. The thyroid gland and pituitary gland had a normal structure. The sternal marrow presented normal appearing hemopoietic tissue with normal proportions of cells of the erythroid, myeloid, and megakaryocytic series.

In the brain there was moderate vascular congestion with a few small perivascular hemorrhages. There was slight hemorrhage in the subarachnoid space about the base of the brain, and this was accompanied by a mild lymphocytic infiltration.

A section through the umbilicus showed only thrombosis of the large vessels, and minimal acute inflammatory infiltration of the segment of necrotic umbilical cord.

Sections of the liver and kidneys were stained by the Dieterle and Levaditi silver impregnation methods. Rare leptospiras were found in the liver. Several typical organisms were demonstrated in the renal tubular lumens. Some of these had an "S" or "C" shape. These organisms could not be photographed satisfactorily. In the tubular cells and lumens were many silver-impregnated structures which were consistent with fragmented leptospiras.

The mother's blood type was 4 O Rh_1Rh_1 (Hr′ neg.), the father's type was 2 A Rh_1rh (Hr′ pos.), and the infant's type was 4 O Rh_1Rh_1 (Hr′ neg.). There was no agglutination of the infant's red blood cells (obtained at autopsy) by the mother's serum when the cells were suspended in saline, bovine albumin, or AB plasma.

Since the microscopic appearance of the hepatic and renal tissues was consistent with the lesions of human leptospirosis, and also because the appearance was almost identical with the lesions of several cases of canine leptospirosis being examined in the laboratory during the same period, agglutination tests with the mother's serum and two strains of Leptospira were done at the Hooper Foundation, University of California Medical School, by Dr. B. Eddie. The results were reported by her as follows:

DATE	STRAIN	TITER			
June 2, 1947	*L. icterohemorrhagia*	1:10,000	1+		
	L. canicola	1:1,000	4+	1:10,000	1+
June 14, 1947	*L. canicola*	1:2,560	4+		
Sept. 9, 1947	*L. icterohemorrhagia*	Negative			
	L. canicola	Negative			
Dec. 29, 1947	*L. icterohemorrhagia*	Negative			
	L. canicola	Negative			

The mother's postpartum course was entirely uneventful. In 1947 to 1948, the patient had a second normal pregnancy, and on July 26, 1948 delivered a normal male infant who remains alive and well. There was no agglutination of either *L. icterohaemorrhagiae* or *L. canicola* by the mother's serum or by serum from the infant's cord taken at the time of birth. (Dr. B. Eddie).

COMMENT

Costa and Troisier,[6] and later Takagi,[7] showed that Leptospira could penetrate the placenta of guinea pigs. Hiyeda[5] reported a case of abortion of a 4-month-old fetus by a woman who had been ill with Weil's disease for twenty days. While both the fetus and its cord were icteric, histopathologic examination of the fetal tissues showed no lesions, and no leptospiras were demonstrable. That author believed, however, that the fetus was infected. Saenz[8] and Das Guptas[4] both were able to demonstrate in guinea pigs the transmission of Leptospira from the mothers to their fetuses; organisms were found in the fetal tissues.

In the case herein reported, the histopathologic lesions in the infant's tissues were typical of those of leptospirosis as may be seen in the human, canine, and bovine forms of the disease.[1, 3] The severe hepatic necrosis, the renal tubular degenerative lesions, and the multiple hemorrhages in many tissues are characteristic of the process. Leptospiras were demonstrated in the infant's liver and kidneys.

That the infant was infected before birth is indicated by the following: (a) the hepatic lesion was too extensive and severe to have developed in the forty-four-hour period following birth, (b) the vernix caseosa and amniotic fluid were stained with bile, and (c) the presence in the mother's serum of agglutinating antibodies in high titers to both *L. icterohaemorrhagiae* and *L. canicola* two weeks after delivery, with their subsequent decrease and final disappearance during the next few weeks. It seems most probable that the mother had latent leptospirosis during late pregnancy. The complete lack of clinical manifestations in her suggests that the fetal tissues were more susceptible to invasion than were the maternal ones. Had the correct pathologic diagnosis in the infant been made promptly, a search for Leptospira in the mother's blood and urine might have been done. The source of infection in this case remains unknown.

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Clinical Conference

CONFERENCE AT THE MT. SINAI HOSPITAL, NEW YORK, N. Y.

DR. JEROME L. KOHN JUNE 24, 1948
DR. SAMUEL KARELITZ AUG. 26, 1948

Case 1. Diaphragmatic Paralysis Associated With Erb's Palsy

DR. ROBERT D. LONDON (Resident in Pediatrics).—On March 17, 1948, a 6-week-old white male infant was admitted to The Mount Sinai Hospital because of intermittent cyanosis, rapid respirations, difficult feeding, and vomiting of six weeks' duration. He was born at term of a primiparous mother. The pregnancy was uncomplicated. The labor lasted twenty-one hours and the child was extracted from the breech position by forceps application to the aftercoming head. His birth weight was 3.1 kg. The child required artificial respiration for ten minutes. A flaccid paralysis of the right arm with slight movement of the fingers and wrist was noted at birth. He remained in the hospital for five days, during which time tachypnea and fatigability on feeding necessitated the use of a Breck feeder. A roentgenogram of the chest on the third day revealed a slightly elevated diaphragm on the right side but no other abnormalities.

At home he fed poorly, was tachypneic, and vomited frequently in a nonprojectile manner both during and shortly after feedings. At 3 weeks of age he was admitted to a hospital because of vomiting and tachypnea. After ten days he was discharged home without a diagnosis and without alteration of symptomatology. In the next ten days respiratory difficulty became severe and cyanosis became constant. He presented no other respiratory symptoms except for mild cough associated with fever which lasted one day. His weight remained stationary since birth.

On admission to the hospital he appeared critically ill and was deeply cyanotic. He was poorly nourished and his skin was pallid. Respiratory distress was prominent with substernal retractions and a rate of 80 per minute. Respiratory excursions on the right were less than those on the left. There were no abnormalities of the head, eyes, ears, nose, or throat. Paradoxical diaphragmatic movement of the right side with deep subcostal retraction during inspiration was noted. Hyperresonance was elicited anteriorly above the fourth intercostal space and posteriorly above the level of the midscapula. Below these regions dullness was obtained. A few fine inspiratory crackles were heard below the right scapula and over the anterior lung field to the anterior axillary line; posteriorly resonance was somewhat diminished. Breath sounds were diminished throughout, with fine inspiratory crackles over the left lower lobe posteriorly. The heart sounds were of maximal intensity in the left anterior axillary line. No abnormal heart sounds were heard. The right arm moved poorly, slight flexion was noted at the elbow, and a fist could be made.

Fluoroscopy of the chest revealed the heart and mediastinum to be displaced to the left. Paradoxical motion and elevation of the right diaphragm associated with shift of the mediastinum to the left on inspiration was evident. The right lung appeared hyperaerated and the left lung was diffusely hazy.

A chest film revealed an extreme degree of elevation of the right diaphragm which extended upward to the level of the fourth intercostal space posteriorly. The liver was displaced upward and medially; distended coils of bowel extended upward along the lateral portion of the right diaphragm. The heart and mediastinal structures were displaced into the left chest.

It was felt at that time that the child had an injury involving the roots of the phrenic nerve and upper portion of the brachial plexus which probably was secondary to the trauma of birth.

He was kept in an oxygen tent continuously from the time of admission, but despite this he remained tachypneic until he expired forty-four days later. The respiratory rate varied, but was most commonly from 60 to 80 per minute. Because of this accelerated rate, feeding was a persistently difficult problem. This was further aggravated by displacement of the stomach and a tendency to swallow and accumulate air which made vomiting a frequent hazard. Gavage feedings were employed and a thickened formula was used. Despite an adequate caloric intake and the retention of feedings throughout most of his course, he gained only 0.25 kg. Repeated examinations of the chest failed to show any significant alteration of the findings noted on admission. The right lung remained partially aerated and the shifted mediastinum encroached on the left chest, which prohibited proper aeration of the left lung. Attempts were made to improve this situation by varying the position of the child, but were to no avail.

The Erb's palsy at no time showed evidence of improvement. The hand was weakly clenched occasionally in a fistlike manner and there were weak flexion movements of the wrist and elbow.

During the course of the illness he was given penicillin prophylactically with success, although repeated white blood cell counts showed intermittent leucocytosis with a differential shift to the left. He remained afebrile throughout his course.

Beginning about twelve days before his death occasional rapidly developing periods of deep cyanosis associated with the regurgitation of small amounts of formula into the oropharynx occurred. The episodes were readily terminated by aspiration of the material.

On the forty-fourth hospital day he suddenly went into collapse. On this occasion aspiration of the mouth and oropharynx produced no exudate or vomitus. Examination of the chest revealed dullness to percussion everywhere with absent breath sounds over the entire right lung field. A total atelectasis of the right lung and a diffuse pneumonia of the left lung were suspected. He became progressively apathetic and expired.

Post-mortem examination by Dr. L. Turner and Dr. M. Baxt, including a dissection of the brachial plexus on the right side and the spinal cord, revealed the following findings.

The anterior roots of C5 and C6 on the right were found avulsed at their junction with the cord. The branches of the brachial plexus and both phrenic nerves were dissected in their entirety and appeared grossly intact. The major portion of the right phrenic nerve arose from C5, receiving a small twig from C4. The right leaf of the diaphragm was elevated to the level of the second rib and it was stretched, thinned, translucent, and contained a sparse amount of muscle fibers. The right lung was almost entirely atelectatic and the left lung contained focal areas of atelectasis. There was no evidence of pneumonia. The heart weighed 34 grams (normal 23 grams) and there was evident a generalized myocardial hypertrophy.

Fig. 1.

Weil-Weigert myelin sheath stains disclosed a complete absence of myelin in the right phrenic nerve and an almost complete absence with a few intact fibers in the right musculocutaneous nerve.

The right leaf of the diaphragm contained markedly atrophic musculature with hyaline degeneration and loss of striation of the muscle fibers. The right lung was markedly atelectatic and the left lung contained focal areas of atelectasis.

DISCUSSION

This case is essentially similar to other instances of diaphragmatic paralysis associated with Erb's palsy. The history of a difficult delivery, Erb's

palsy noted at birth, and respiratory difficulty developing at or shortly after birth are frequently described features. These, plus the fluoroscopic findings of an elevated diaphragm and paradoxical respirations, make the diagnosis of phrenic nerve injury almost certain. The most common diagnostic errors are congenital heart disease, pneumonia, intracranial hemorrhage, atelectasis, congenital malformations of the respiratory tract, and diaphragmatic hernia.

With adequate medical care which is primarily prevention of infection and aspiration and the administration of oxygen as indicated, about 80 per cent of the infants recover.

Usually the injury consists of stretching or pressure on the phrenic nerve root. Avulsion of nerve roots as was found in this case here described has not been noted. It is, therefore, unknown whether infants recover after such extensive damage.

DR. KOHN.—Is there any useful surgical procedure to alleviate or correct the altered physiology this condition produces?

DR. LONDON.—A discussion with thoracic and pediatric surgeons about this problem failed to reveal any known surgical technique to handle the problem.

DR. MOLOSHOK.—Is the diaphragmatic paralysis always associated with an Erb's palsy?

DR. LONDON.—A review of thirty-two described cases disclosed that twenty-two were associated with Erb's palsy and ten were not.

DR. KARELITZ.—Do you often find complete avulsion of nerve roots associated with this injury?

DR. LONDON.—A search of the literature failed to uncover a similar case.

DR. KOHN.—Is this injury always associated with breech deliveries?

DR. LONDON.—To the best of my knowledge, yes.

SUMMARY

DR. KARELITZ.—In summary, this is a case of Erb's palsy and diaphragmatic paralysis due to trauma of the brachial plexus with avulsion of the phrenic nerve from its roots. It was incurred in the extraction of the child in breech position. While the child manifested respiratory difficulty early, it became severe after infections set in. All therapy was without avail.

We have been unable to find record of other cases of phrenic nerve palsy in the newborn infant in which complete avulsion of the nerve roots was demonstrated.

Case 2. Bleeding Peptic Ulcer

DR. BENNETT L. GEMSON (Assistant Resident in Pediatrics).—This was the first Mount Sinai Hospital admission of a 5½-year-old white boy who was well until ten days prior to admission, when he developed a mild, nonbloody diarrhea associated with vomiting and a temperature of 101.8° F. A younger brother had diarrhea just prior to this illness, the patient's mother developed

diarrhea coincidentally with the patient, and the father developed this same symptom one week later.

The patient's diarrhea and fever subsided in one day after he was given Peptobismol and a "chalk" medicine. During this episode, however, and in the following five days, the patient had recurrent bouts of moderately severe, midline, abdominal pain; the pain would subside spontaneously, and was frequently associated with nausea, but never with vomiting. The patient was constipated after the diarrhea, and so, seven days prior to admission, was given two tap water enemas with return of a few small, hard, fecal masses. The following day, six days prior to admission, he was given milk of magnesia and two days later, four days prior to admission, castor oil, with a temperature elevation that evening to 101° F. Early the next morning, three days prior to admission, the patient had a large, nonbloody, liquid bowel movement followed by weakness and subsequent passage of three loose movements containing bright red blood in moderate amount. The fever then subsided, as did the abdominal pain. For two days prior to admission there still were frequent, tan-colored stools which did not contain gross blood; however, when the patient's perianal region was wiped there was bright red blood on the paper. Concomitantly the patient showed progressive asthenia and pallor, and on the day prior to admission he developed some pain in the neck, ringing in the ears, and swelling around the eyes, with a temperature rise to 104° F.

There was no previous history of anemia, hematemesis, melena, trauma, ingestion of foreign material, or bleeding tendency in the patient or his family.

Family history was noncontributory, and review of systems was negative.

Physical examination revealed a well-developed, well-nourished white boy, somewhat disoriented, with marked pallor, cold, clammy skin, and rapid, thready pulse, presenting a picture of circulatory collapse. The pulse rate was 180 per minute, and the blood pressure 106/0. Because of the patient's critical condition further examination was necessarily brief. The lungs were clear to percussion and auscultation. The heart showed marked tachycardia. Sounds were of fair quality, and there were no murmurs. On careful abdominal palpation no liver, spleen, or other masses were palpated.

Significant laboratory findings were: hemoglobin, 2.75 Gm.; white blood cells, 27,000; segmented polymorphonuclear leucocytes, 60; nonsegmented polymorphonuclear leucocytes, 12; lymphocytes, 28. The blood smear showed two normoblasts per 100 white blood cells, moderate aniso- and poikilocytosis, but no abnormal cells. The urine was negative. The blood group was A, Rh positive. The bleeding time was 4 minutes and the clotting time 3.5 minutes.

The patient was given nothing by mouth, and sedated with codeine and phenobarbital by injection. He was placed in an oxygen tent, and a blood transfusion was started.

After receiving 100 c.c. of blood, the patient appeared somewhat improved, with a rise in blood pressure to 130/80 and a fall in pulse to 144. Six hours after admission the hemoglobin had risen to 9.5 Gm. At this time profuse rectal bleeding with a large number of clots was noted. Another 500 c.c. of blood was given, together with 5 c.c. of calcium gluconate.

During the second hospital day there were four episodes of massive rectal bleeding. The hemoglobin fell from 9 to 6 Gm. with 2,260,000 red blood cells, and a fourth transfusion of 500 c.c. was given. The blood pressure ranged between 110/50 and 130/80, and the pulse between 136 and 150. The patient was restless and crying most of the day.

On the third hospital day, the patient continued to pass large, liquid, bloody stools, and the hemoglobin had fallen to 5 Gm., with 48,000 white blood cells. A fifth transfusion of 500 c.c. was started. Because bleeding was uncontrolled after three days of conservative treatment, he was seen by a surgeon, who felt the most likely causes of his bleeding were (1) a polyp of the large bowel, (2) a bleeding Meckel's diverticulum, or (3) a reduplication of the intestine with bleeding from the reduplicated loop. Bleeding peptic ulcer was thought to be unlikely in view of lack of vomiting or hematemesis. Exploration was advised.

The patient was given an additional 500 c.c. of blood, and taken to the operating room shortly after noon.

The abdomen was explored through a right midrectus incision. There was a small amount of clear amber fluid in the peritoneal cavity. The intestinal tract from the lower sigmoid up to the upper third of the ileum was filled with darkly colored blood. It was difficult to ascertain with certainty whether there were any polyps in the colon or sigmoid due to the blood in the bowel. There was no evidence of a Meckel's diverticulum or of an intestinal reduplication. The stomach was visualized. It did not contain blood and felt normal. The head of the pancreas felt slightly enlarged and hard, as is average in a child of this age. The duodenum was palpated but not visualized, and although the pylorus felt slightly indurated there was nothing to suggest by palpation that an ulcer was present.

Postoperatively, bloody drainage was obtained from the Levin tube and the patient continued to have bloody stools. After an additional 500 c.c. of blood, his hemoglobin was only 6 Gm.

On the fourth day (the first postoperative day), bloody drainage per Levin tube and per rectum continued, and the patient appeared worse. The blood pressure fell to 98/0 with a pulse rate of 164. After receiving 1,200 c.c. of blood, the hemoglobin was 5 Gm. Two more 500 c.c. blood transfusions raised the hemoglobin to 9 Gm. and the blood pressure to 140/70. He was offered small amounts of skimmed milk by mouth. In the late afternoon he passed a polypoid mass by rectum, measuring about 1½ by 1½ cm., lobulated and yellow stained. Pathology report after examination of a frozen section was necrotic tissue, possibly a polyp, but it was not possible to state its origin with certainty. This finding, although not definite, made us feel that we were dealing with a case of multiple polyps; otherwise, a second exploration might have been attempted.

On the fifth day (the second postoperative day), bleeding per rectum continued, and the patient was extremely restless. He received 1,500 c.c. of blood, yet his hemoglobin never rose above 6 Gm. The blood pressure ranged

between 100/40 and 132/70. Toward evening he had his first episode of hematemesis, vomiting about 60 c.c. of bloody fluid.

During the sixth day (the third postoperative day), his condition deteriorated. There were frequent hematemeses and bloody stools. He was sedated heavily, given Hykinone, ascorbic acid, and calcium by mouth, and received two additional transfusions. His hemoglobin ranged between 5.5 and 6.0 Gm., blood pressure between 120/40 and 100/0, and pulse between 180 and 200. Toward evening he appeared confused. Surgery was not considered indicated.

On the seventh day (the fourth postoperative day), bleeding per rectum persisted. Early in the morning the patient's pulse was rapid and thready, and the respirations were increased. He began to vomit large amounts of bright red blood and passed continual dark red liquid per rectum. At 5:45 A.M. respirations ceased. He had received a total of 7,820 c.c. of blood and a host of medicaments in an unsuccessful effort to control his gastrointestinal bleeding, whose source remained a mystery up to the time of death.

DR. KARELITZ.—What were the findings at post-mortem?

DR. GEMSON.—At post-mortem, examination of the unopened stomach and duodenum failed to reveal any abnormality, but with these organs open an acute peptic ulcer of the duodenum was found, with erosion of the superior pancreaticoduodenal artery. There was a large amount of blood in the gastrointestinal tract. The tissues were moderately icteric. There was 400 c.c. of fluid in the peritoneal cavity and 300 c.c. in each pleural cavity. There was a focal fibrinous pleuritis of the right lower lobe, partial atelectasis of all lobes of the lung, and petechial hemorrhages of the lungs and pericardium.

Of particular interest in this case were: (1) the difficulty in making a proper diagnosis, (2) the failure of conservative treatment in controlling the bleeding, and (3) the inability to locate the source of the bleeding at exploratory laparotomy and (4) the inability to diagnose the presence of the ulcer at post-mortem examination of the unopened stomach.

Dr. Nathan Schifrin, Assistant Resident on Pediatrics, who admitted this patient, ventured an admission diagnosis of "possible peptic ulcer with hemorrhage." Other members of the Pediatric Staff were less specific and offered the possibilities of a bleeding ulcer of Meckel's diverticulum, a bleeding polyp, and a bleeding gastric or duodenal ulcer as the most likely diagnoses. The surgeons felt that the absence of hematemesis until the terminal stages of hemorrhage made peptic ulcer of the stomach or duodenum improbable.

DR. LONDON (Resident on Pediatrics).—The appearance of bloody drainage via the Levin tube postoperatively might have led one to suspect that the source of the bleeding was high up in the gastrointestinal tract, stomach, or duodenum.

DR. KARELITZ.—I believe that Dr. London is correct, but the passing of the polyplike mass confused the issue. Would you say a few words about the occurrence of peptic ulcer in childhood?

DR. GEMSON.—Peptic ulcers of the stomach and duodenum, although rare, may occur at any age and have been described in stillborn and even premature infants. They are more numerous in infancy than in childhood, and tend to run a more acute course than they do in adult life.

Ulcers are asymptomatic in a high percentage of cases, and are frequently unsuspected until autopsy examination. A silent clinical course is the rule in infancy, but after the first year or two symptoms are similar to those of adults.

Ulcers in the young may give rise to (1) malnutrition and repeated gastric upsets, (2) exsanguinating and even fatal hemorrhage, (3) perforation, and (4) mechanical obstruction from scar tissue near the pylorus.

Treatment is much the same as in adults. Medical treatment usually effects a cure in uncomplicated cases. Hemorrhage is usually tolerated poorly, and blood should be administered sooner and more liberally than is the custom with adults.

Surgical treatment consists of gastroenterostomy for mechanical obstruction, simple closure for perforation, and ligation of the bleeding vessel (if it can be located) for hemorrhage.

DR. ANFANGER.—What are the conditions most likely to cause massive gastrointestinal hemorrhage via the rectum?

DR. GEMSON.—A bleeding Meckel's diverticulum, a polyp anywhere in the colon, and a peptic ulcer are the most probable causes of profuse hemorrhage from the gastrointestinal tract, aside from hematologic disorders which could be readily diagnosed by appropriate blood studies. Esophageal varices, as well as peptic ulcer, almost invariably produce hematemesis.

DR. E. GOODMAN.—I have reviewed the records at Babies' Hospital and found reference to three cases of duodenal ulcer in children, all occurring at 11 to 12 years but with histories dating back to 8 years of age.

I am surprised that the children who bled did not vomit blood.

DR. KARELITZ.—In the past two years I have had the rare opportunity to see four cases of duodenal ulcer in childhood. The first patient, a boy of 13, fainted while standing in the food line at school and did the same the next day. His hemoglobin was 6 Gm. and the stools were tarry. He did well on bed rest, two transfusions, a residue free diet, and alkali. He has had no recurrence of symptoms to date. This boy had epigastric discomfort a year before his bleeding episode, and was told by a doctor to take bicarbonate of soda. Finding relief, he did not complain again but took bicarbonate of soda when pain recurred. He also learned that eating relieved him of his pain.

The second was a boy of 14 years who, while returning from a ranch in Wyoming, vomited all his meals on the train and continued to vomit everything ingested for the next seven days. He had slight tenderness in the epigastrium on physical examination. Radiologic examination revealed some pyloric stenosis and a duodenal ulcer. Gastric contents contained blood. He, too, has done well on a dietary regime.

The third was a 16-year-old girl who fainted while studying. She was found to be pale, her hemoglobin was 6.5 Gm., and the stools were tarry.

There had been no history of abdominal pain nor of dyspepsia. She had dieted severely for some time and had lost 35 pounds. She did well on a low residue diet with alkali.

The fourth was the patient described here by Dr. Gemson.

Thus only one of the four vomited. Of the three who bled, none vomited. The histories of all four children reveal domestic disturbances which resulted in behavior defects.

In the previous twenty years of my pediatric practice I never have had a case of duodenal ulcer. Gastroenterologists are prone to think that duodenal ulcer has its incipiency in childhood. Can it be that the world turmoil is affecting our youth to the extent of helping to produce more psychosomatic diseases such as duodenal ulcers?

Case 3. Acute Idiopathic Hemolytic Anemia With Hemoglobinuria

DR. NATHAN SCHIFRIN (Assistant Resident in Pediatrics).—This is the first Mount Sinai Hospital admission of a 23-month-old male child brought here because of dark urine of three days' duration. The child was apparently well until three days ago when he had one episode of vomiting. Following this the child had a shaking chill and a temperature elevation to 101° F. One-half an Empirin compound tablet was given. Because of constipation for over forty-four hours he was given a soapsuds enema. Late that afternoon dark urine was passed. The pediatrician was summoned and on physical examination acute follicular tonsillitis was noted. Penicillin 25,000 units every three hours was started intramuscularly. The finding of acute tonsillitis and the history of dark urine made the physician suspect acute nephritis. The white blood count was 8,900 per cubic millimeter, the hemoglobin was 8.5 Gm. per 100 c.c. The temperature returned to normal about twelve hours after the starting of the penicillin therapy, but the urine continued to be dark. A urine specimen obtained the next day contained laked red blood cells and granular casts. Several other urine specimens were examined with the same findings. It was felt that there were not enough red blood cells to account for the dark color. Spectroscopic examination of the urine by Dr. Daniel Stats showed hemoglobin and methemoglobin to be present. On the day before admission the white blood count was 5,050, and hemoglobin was 7.0 Gm. The smear showed rare spherocytes and the reticulocyte count was 5 per cent. Slight icterus of the sclerae was noted on this day. The patient was passing urine frequently, but only 15 to 30 c.c. at a time. He was anorectic, his pallor was increasing, and he continued to pass dark urine. He was, therefore, hospitalized. There was no family history of allergy, no new foods had been included in the diet, no unusual medication had been tried before the onset of this episode, and the patient had had Empirin compound tablets before without any ill effect. There was no history of having ingested any fava beans. The mother's blood Wassermann was negative at the time of this child's birth.

On admission the patient, a well-developed, and well-nourished child, was acutely ill but in no distress. He appeared very pale and presented a lemon

yellow appearance. The sclerae were slightly icteric. The tonsils were enlarged and a white exudate was present on the left. The cervical lymph nodes were shotty in the anterior and posterior cervical chains bilaterally. The lungs were clear to percussion and auscultation. A short systolic murmur was heard at the apex. The liver was palpable one centimeter below the costal margin. The spleen was not palpable. He was afebrile.

On admission the red blood count was 2.5 million with 7.0 Gm. of hemoglobin. White blood count was 10,500 and the platelets were 150,000. The patient's blood type was group A, Rh positive, Rh′ positive and Rh″ negative. Hypotonic saline fragility test of the patient's red blood cells revealed hemolysis starting at 0.44 per cent saline and complete at 0.16 per cent saline. Heat resistance test for paroxysmal nocturnal hemoglobinuria was negative. Examination of the patient's serum for agglutinins revealed no agglutination in albumin or saline at 37° C. against homologous red blood cells. At 4° C. there was a titer of agglutinin of 1:10 against homologous red blood cells. Against heterologous compatible red blood cells at 37° C. there was no agglutination in albumin or saline; at 4° C. the titer of agglutinins was 1:20. Thus, no significant rise in agglutinin titer was demonstrable. There were no hemolysins against compatible red blood cells. The Donath-Landsteiner test was negative. The course of illness, the normal red blood cell fragility, the negative heat resistance test, the hemoglobinemia, and hemoglobinuria made the diagnosis of acute hemolytic anemia of unknown etiology most probable.

The patient was promptly transfused with 400 c.c. of concentrated blood of group A, Rh_0 Rh′ without a transfusion reaction. During the first eighteen hours in the hospital he passed dark urine five times, the volume varying between 20 and 60 c.c. on each occasion. The urine hemoglobin content varied between 135 and 400 mg. per cent. All the dark urines contained both oxyhemoglobin and methemoglobin on spectroscopic examination. The icteric index, by the alcohol method was 10 and the quantitative hemoglobin in the plasma on admission was 120 mg. per cent. Both oxyhemoglobin and methemoglobin were present in the plasma. Kidney function was maintained for the specific gravity of the dark urines was 1.028 to 1.030. For the first eighteen hours in the hospital albumin was present in the urine and the urobilinogen titer was less than 1:10. About eighteen hours after the transfusion was started the urine became lighter in color. The albumin content diminished and finally disappeared. As the urine became lighter the urobilinogen titer rose from 1:10 to 1:80 and hemoglobinuria disappeared.

Twenty-four hours after transfusion the red blood count was 3.88 million and the hemoglobin was 10 Gm. Two days after transfusion the hemoglobin was 11 Gm. and the reticulocyte count was 2 per cent. The patient was discharged on the fifth hospital day with a hemoglobin of 10 Gm. and a red blood count of 3.85 million.

CHAIRMAN.—Dr. Stats, would you like to comment on this case?

DR. STATS.—This case is a typical example of a relatively mild hemoglobinuric episode of unknown causation which, while rare, is much more often encountered in early childhood than at other periods of life. In our experience such disorders are transient and recovery is to be anticipated after one or several blood transfusions. We have not encountered transfusion reactions in any unusual frequency in such cases if properly grouped and matched blood is given. We believe that the occurrence of hemoglobinuria and/or hemoglobinemia is a contraindication to splenectomy. Upon this finding alone we would divide hemolytic anemias into those in which splenectomy is valueless and those in which it may prove successful in bringing about a prompt cessation to excessive hemolysis. In acute idiopathic hemolytic anemia with hemoglobinemia the duration of rapid blood destruction is generally short-lived, lasting for four or five days. Once hemoglobinuria disappears it is not likely to reappear. Blood regeneration may be slow for a period as long as one month before restitution to normal in the blood figures occurs. Recurrences are rare.

DR. KARELITZ.—Dr. Schifrin, would you tell us what is concentrated blood?

DR. SCHIFRIN.—The concentrated blood used in this case was made by removing 100 c.c. of plasma from 500 c.c. of citrated whole blood.

DR. KOHN.—Was a Wassermann done on this patient?

DR. SCHIFRIN.—The mother had a negative Wassermann during the third trimester of this pregnancy.

DR. BLUMENTHAL.—How is the heat resistance test done and what is its significance?

DR. STATS.—The heat resistance test is performed by allowing the patient's blood to clot and remain at 37° C. for six hours. The presence of gross hemoglobin in the serum is a positive result and definitely indicates the presence of paroxysmal nocturnal hemoglobinuria.

DR. REUBEN.—Does blood serve as a replacement or does it in some way stop the hemolytic process in this disease?

DR. STATS.—That is a very difficult question to answer. It is probable that the blood acts only as replacement. In one case I observed, hemoglobinuria was diminishing before the blood transfusion was given.

DR. KARELITZ.—How does this differ from paroxysmal hemoglobinuria and why could this not be the original episode in a case of paroxysmal hemoglobinuria?

DR. STATS.—There are three types of paroxysmal hemoglobinuria: (a) syphilitic paroxysmal cold hemoglobinuria which was excluded by the negative Donath-Landsteiner test and absence of clinical evidence of syphilis; (b) hemoglobinuria due to cold hemagglutinins excluded by the low titer of cold hemagglutinins; (c) paroxysmal nocturnal hemoglobinuria excluded by the negative heat resistance test.

In summary, this 23-month-old male child developed an episode of severe hemolysis with hemoglobinuria and methemoglobinuria, and jaundice in the course of an infection, follicular tonsillitis. The process stopped after a transfusion of 400 c.c. This is considered to differ from paroxysmal hemoglobinuria by having a negative Donath-Landsteiner, negative heat resistance tests, and a very low titer of cold hemagglutinins.

Case 4. Mercury Poisoning

DR. RICHARD N. REUBEN (Assistant Resident in Pediatrics).—The patient was a 5-year-old white girl who was perfectly well until she swallowed a 0.5 Gm. tablet of bichloride of mercury. At the time of the mishap, the patient and her family were living in rural upstate New York, in a large house of which only a portion was in constant use. The child had been wandering one morning through the unused section when she discovered a bottle left on a shelf and swallowed one of the characteristic blue coffin-shaped tablets of mercuric chloride it contained. (The bottle was labeled "Poison.")

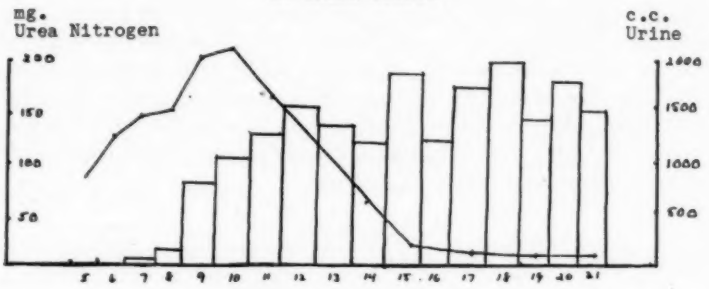
The patient soon afterward complained to her mother of a peculiar sensation in her mouth and the mother, on eliciting the story and identifying the bottle, gave the patient some milk and egg yolks. This was promptly vomited, the vomitus also containing some blood-streaked mucus and a small portion of the tablet. Because of persistent vomiting for about four hours, she was taken into town to see the doctor, who referred her to a second physician. Frequent small feedings of milk, repeated small tap water enemas, and sedation were prescribed. The child, however, continued to vomit and the enema returns were tarry and mucous-containing. Toward the end of the day she developed a diarrhea consisting of loose, green-black, mucus laden stools, but during the first day she apparently voided normally.

On the following day because of the recurrent vomiting and diarrhea, she was hospitalized in a nearby city. She voided a small amount of urine in the morning but was anuric for the remainder of the day. The next day, because of inability to retain oral feeding, she was given a clysis. The vomiting ceased and the diarrhea slackened. The patient remained anuric, and for the first time seemed lethargic. On the fourth day, parenteral fluids were given intravenously and by clysis (amount and type not known). The anuria persisted. BAL was administered in dosage described by attending physician as usual therapeutic amount. The lethargy seemed more pronounced although the patient seemed in generally good condition, and at this point the patient was transferred to the Mount Sinai Hospital where she arrived on the fifth day of her illness, having been anuric for about three days.

On admission the patient apppeared listless but in no distress. The face was puffy. The skin turgor was good. The tongue borders were gray with tiny ulcerations and the mucous membranes of the mouth were red and slightly edematous. The pharynx was mildly injected. The lungs were clear and the heart appeared normal. The abdomen was soft and nontender. The kidneys were not felt and there was no costovertebral angle tenderness. Extremities

were normal. Blood pressure was 110/72, pulse 100, respirations 35, hemoglobin 8.1 Gm., and hematocrit 21 per cent. White blood count was 12,500, polymorphonuclear cells 77, lymphocytes 23. Blood urea nitrogen was 79, CO_2 content 34 volumes per cent, creatinine 17.7, uric acid 7.3, calcium 9.7, phosphorus 4.7, sodium 132 meq., chloride 90 meq., total protein 5.1 per cent, cholesterol 170 mg. per cent, Wassermann negative, ECG no abnormality.

CHART SHOWING RELATION OF BLOOD UREA NITROGEN LEVELS TO URINE OUTPUT



Daily urine volume in cubic centimeters.

Blood urea nitrogen in milligrams per 100 c.c.

* Patient entered Mount Sinai Hospital on fifth day of illness. History indicated that patient had voided normally on first day, then had been oliguric on second day and anuric on third and fourth days.

Chart I.

The patient was placed on a regimen of restricted fluid intake consisting of 300 c.c. of sweetened fruit juices daily, the amount subsequently varying with gain or loss in weight. One hundred and fifty thousand units of Procaine-Penicillin were given daily prophylactically. The child remained lucid and comfortable, and sat up in bed. She took fluids poorly and continued to have watery brown stools for a week. She remained anuric for two more days or a total of five days. There were two succeeding days of oliguria (less than 125 c.c.) and then on the fifth hospital day or eight days after the onset of oliguria-anuria, the urine volume returned toward levels of 1,000 to 1,500 c.c. daily. Coincident with the return of increased urinary output the patient lost ten pounds over a period of a week. The urine at first was of low specific gravity (1.010 to 1.012) and contained occasional granular and hyaline casts and occasional white blood cells, but at the time of discharge, two and one-half weeks later, the sediment was negative and the specific gravity had risen to 1.020 on concentration test. Meanwhile the blood urea nitrogen had risen to

a high of 222 mg. per 100 c.c. on the tenth day of the illness but declined rapidly reaching normal levels by the sixteenth day. There were no significant changes in the carbon dioxide content of the blood.

With the return of urinary flow, the remainder of the course was uneventful. As the urine volume increased, the intake of oral fluids was raised so that it approximated the loss of fluid in the urine. The sodium chloride content of the urine was also measured, and an attempt was made to insure adequate replacement in the diet. During the first week of diuresis, the patient lost between 1 and 3 Gm. daily and salt in about the same amount was added to the food tray (on bread and butter, in tomato juice, etc.). The patient had some transient difficulty in retaining solid foods and the stools continued to have excessive amounts of mucus for about two weeks after onset of illness. Because of an anemia of 6.0 Gm. of hemoglobin occurring at the end of the third week of illness, the patient was transfused and thereafter maintained a hemoglobin over 10.0 Gm. The blood pressure, fundi and other physical findings had remained normal throughout the illness.

DISCUSSION

DR. ANFANGER.—How does BAL act in mercury poisoning?

DR. R. N. REUBEN.—BAL or British Anti-Lewisite is a compound containing two sulfhydryl (-SH) groups. Experimentally it has been shown that arsenic, mercury and other heavy metals produce toxic effects in the body by combining with the sulfhydryl groups of body protein and that BAL competes successfully with the protein to combine with the heavy metal. Although BAL may actually absorb some of the heavy metal already combined with protein, it is much more efficacious to provide BAL before the heavy metal has a chance to combine with body protein. Consequently the best results are obtained where BAL is given early, especially within three and one-half hours. It is given as a 10 per cent solution in peanut oil intramuscularly, and an accepted regimen is to give 5 mg. per kilogram of body weight initially, repeating a dosage of 2.5 mg. per kilogram at 1 to 2, 2 to 4, and 6 to 12 hours the first day. On the second day 2.5 mg. per kilogram is given twice and thereafter once daily for two or three days.

DR. KOHN.—Dr. Mann, you had an opportunity to study a series of cases of mercury poisoning some time ago. Would you discuss some of the methods used in treatment and the results obtained?

DR. L. T. MANN.—I had occasion to collect thirty cases of mercury bichloride poisoning from the records of Mount Sinai Hospital admissions from 1914 through 1935.

Three patients had renal decapsulation, and twenty-seven were treated medically by: (1) Attempting to immobilize the mercuric ion with sodium thiosulphate or sodium formaldehyde sulphoxylate, which is a reducing agent; (2) Eliminative treatment as gastric lavage, colon irrigation, and intravenous fluids; (3) Alkalinization and forced fluids; (4) Patterson-Lambert method

which consisted of 8 oz. of milk given every two hours, alkali by mouth, and colon irrigations.

All the patients vomited after taking mercury bichloride so that the amount retained and absorbed could not be estimated in any case. It should be emphasized, however, that the patients who took only one or two tablets, 0.5 to 1.0 Gm. all survived, whereas mortality was seen when 1.5 Gm. or more were ingested.

There were twelve male and eighteen female patients. The ages were from 13 years to 64 years, but the greater majority were in the 20's.

Seventeen took from 0.5 to 1.0 Gm. and, as mentioned, all survived. Twelve took from 1.5 to 3.0 Gm. of whom five survived and seven died. One other patient took 20 Gm., and the outcome was fatal.

In three patients, all female, a bilateral renal decapsulation was made. All of them died. They were anuric for at least three days. We found references to 203 patients who had ingested mercury bichloride and in whom a renal decapsulation had been made. There was a mortality of over 90 per cent.

The duration of the anuria in the fatal cases was from three to eight days. In two children that recovered one was anuric for three days and the other for ten days.

We have had a long follow-up of over ten years on five of our patients. They now all have normal urine and normal kidney function.

DR. J. KOHN.—Dr. Kroop, would you discuss the general management of the renal insufficiency seen in mercurial poisoning?

DR. I. G. KROOP (Dazian Foundation Research Fellow in Medicine).—The chemical and anatomical changes characterizing the acute renal insufficiency of acute mercurial intoxication are reversible. Despite the fact that mercury injures chiefly the proximal portion of the nephron, the disturbances of body equilibrium secondary to the acute uremia of mercurial nephrosis are similar to those of lower nephron nephrosis.

The treatment of the reversible renal insufficiency of mercurial nephrosis is similar to that described for management of renal insufficiency produced by hemoglobinuria. (Kroop, I. G., Fishman, A. P., Leiter, H. E., and Hyman, A.: The management of acute renal insufficiency following transfusion, to be published.) In the case of the latter, management resolves itself into the therapy of three periods: (1) the immediate emergency period following hemolysis; (2) the period of oliguria and anuria; and (3) the period of diuresis and beginning convalescence. This division is applicable to the treatment of mercury nephrosis. The emergency period in acute mercury intoxication requires the treatment of shock if present, and the energetic emergency measures toward the elimination and neutralization of the mercury which is a protoplasmic poison. Immediate effective therapy, as applied in this case, will prevent severe renal damage and will shorten the period of oliguria and anuria. Gastric lavage with protein containing fluids precipitates the mercury.

Colonic irrigations remove the mercury which is excreted into the large bowel. Continued lavage and irrigation beyond the immediate emergency period is not advisable because it might lead to electrolyte and water depletion. BAL (2,3 dimercaptopropanol) should be administered in full dosage within three and one-half hours after the ingestion of the mercury bichloride. It should always be given, even if begun as late as twenty-four or forty-eight hours after ingestion of mercury. BAL combines with mercury, detoxifies it, and aids in its excretion.

The principal aim of therapy during the period of oliguria and anuria of the acute renal insufficiency due to mercury, is the maintenance of fluid, electrolyte, and acid-base balance. Fluid and salt restriction is imperative during this period. Excessive fluid administration will not initiate urine flow and may lead to cerebral and pulmonary edema. Acidosis, if clinically significant should be corrected with alkali by mouth. If alkalinization of the urine is difficult it should not be attempted since it may lead to severe alkalosis. The guiding therapeutic principle in this second period of oliguria and anuria is to prolong the patent's life long enough for tubular regeneration to occur and for diuresis to herald recovery of function. If despite proper management the condition of the patient deteriorates, an artificial means of dialysis may serve as a useful therapeutic adjuvant. Peritoneal lavage (Frank, H. A., Seligman, A. M., and Fine, J.: Treatment of Uremia After Acute Renal Failure by Peritoneal Irrigation, J. A. M. A. **130**: 703-705, 1946), and extra corporeal dialysis of blood with an artificial kidney (Fishman, A. P., Kroop, I. G., Leiter, H. E., and Hyman, A.: Experiences With the Kolff Artificial Kidney, to be published) are the most efficient methods available. These methods, however, are not a substitute for correct medical management.

The aim of therapy during the period of diuresis and beginning convalescence is the maintenance of fluid and electrolyte equilibrium. The loss of excessive quantities of water and salt in the urine may lead to dehydration, acidosis, and recurrent oliguria. Salt retention instead of salt loss may occur in some instances of tubular dysfunction. Under these circumstances, administration of sodium chloride and fluid may lead to pulmonary and cerebral edema. It is clear that chemical determinations of chloride in the blood and urine are essential guides for proper therapy.

This case of acute mercurial nephrosis in a five-year-old girl with complete anuria for five days, and oliguria for three days, illustrates the application of these principles of therapy. Pulmonary and cerebral edema were avoided by restriction of fluid and electrolyte. Dehydration was prevented during the period of diuresis, which began on the ninth day. At no time was there any indication for the use of the artificial kidney. Meticulous medical management, according to the principles outlined above, led to an uneventful recovery.

DR. KARELITZ.—Dr. Sirota, this patient had a renal vein catheterization and kidney function studies just prior to discharge. Would you discuss your findings?

DR. J. H. SIROTA.—The results of the renal function tests performed on the twenty-second day after onset of anuria are tabulated below. The values are based on the clearance techniques of Homer W. Smith.

All figures are corrected for an ideal surface area of 1.73 square meters.

PLASMA CLEARANCES*

	INULIN (C.C./MIN.)	PAH (C.C./MIN.)	T_mPAH (MG./MIN.)	CIN/ T_mPAH	CPAH/ T_mPAH
Twenty-second day from onset of anuria	78.2	236	28.8	2.72	8.22
Normal values	117	594	82.2	1.42	7.25

*T_m, Maximum tubular excretion.
PAH, P-aminohippuric acid.
CPAH, Clearance of P-aminohippuric acid.
CIN, Inulin clearance.

The inulin clearance is usually accepted as the glomerular filtration rate and the PAH (P-aminohippuric acid) clearance as the renal plasma flow through functional renal parenchyma. However, these figures must be interpreted with caution when applied to severely damaged kidneys (Notes on the interpretation of clearance methods in the diseased kidney, Smith, H. W.: J. Clin. Invest. **20**: 631, 1941). Thus, the above value for the PAH clearance of 236 c.c. per minute/1.73 sq. m. cannot be accepted as the renal plasma flow unless it can be shown that under the conditions of the test about 99 per cent of the PAH is removed from the blood during one passage through the kidney. This can only be ascertained by simultaneous sampling of the arterial and venous bloods by renal vein catheterization and arterial puncture. Unfortunately, this was not done with this patient.

The subnormal figures obtained for the ability of the tubules to secrete PAH at high plasma levels (T_mPAH) reflects severe functional damage to the proximal convoluted tubules.

Endogenous creatinine clearances performed on the tenth and fifteenth day of the disease were 4.03 and 4.07 ca per minute respectively. Since the clearance of the substance has been shown to approximate glomerular filtration (The renal clearance of endogenous "creatinine" in man, Brod, J., and Sirota, J. H.: J. Clin. Invest. **27**: 645, 1948), one must assume severe depression of this function or considerable back diffusion of glomerular filtrate through damaged tubular walls. Thus, the anuria and oliguria of this disease may be explained by decreased glomerular filtration and/or marked tubular back diffusion of formed glomerular filtrate.

The elevation of the ratio CPAH/T_mPAH suggests that the tubule cells which are functioning in the proximal convolution are receiving an adequate blood supply.

From past experiences, one may predict the return to normal, in several months, of all functions tested. The inulin and PAH clearances return to normal first, being followed by the T_mPAH and finally by the ability to maximally concentrate urine.

Psychologic Aspects of Pediatrics

HOW CAN NURSERY SCHOOL BE EXPECTED TO BENEFIT A CHILD?

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IF THE conditions are auspicious, nursery school experience can be a salient factor in starting a child on the road to healthy growth and development. It cannot, however, be taken for granted that every nursery school will have positive value for every child. The decision as to whether a particular child shall go to nursery school, and the choice of the school, needs discriminating consideration in terms of (1) the maturity of the child and his readiness to be separated from the home, (2) the nature of the home situation which would be alternate to his attending a nursery school, (3) the qualifications of the staff of the nursery school to meet the growth needs of young children and to handle the special problems which arise when young children spend long periods of time together, (4) the physical set-up of the nursery school and its health standards, and finally, (5) the question as to whether the experience will contribute to the basic happiness of the child.

There are many occasions when the pediatrician is involved in this type of decision. This paper will present, from the point of view of the psychologist, a brief digest of the potential influence of nursery school experience on the development of the child.

PSYCHOLOGIC DEVELOPMENT DURING THE NURSERY SCHOOL YEARS

It is during the period of early childhood that the child becomes aware of himself as apart from other people and lays the foundation for attitudes toward himself as an individual. His energies and curiosities bring him into throbbing contact with his environment and in his pattern of responding to these stimuli he is developing attitudes that will have an important effect on his role as a working adult He faces the dilemma of getting his fill of love and protection and at the same time weaning himself from the infantile dependence which becomes emotionally irksome as his skills, his assertiveness, his individuality all begin to blossom. He needs a basis for differentiating one sex from another, identifying himself with his own sex, and, for the sake of his future happiness in sex and family relations, feeling content with his membership in his own sex. He is formulating his role as a child to his parents and, implicitly, laying the groundwork for the kind of parent he will be to his own children.

He struggles with adapting his own impulses to the requirements of civilization in many guises—toilets, forks, neatness, money, etc. In his long hours of play with other children he is establishing a *modus vivendi* for living with

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other people. He encounters specific forms of restraint and authority and, out of the wide range of possible reactions to authority—cringing, anger, subterfuge, resentment, acceptance—he develops an individual formula compounded of his own temperamental qualities as well as the quality of authority which he experiences. He experiences denial, frustration, loneliness, fear, pain, anger, and out of all this emotional weathering his own style of endurance and feeling begins to take shape.

TECHNIQUES AND EQUIPMENT IN THE NURSERY SCHOOL

The nursery school, as an educational institution, has an important function in helping young children come to grips with these major life-problems of their early years. This is accomplished partly by the program of activities in which the children engage and the experiences which are provided for them. More important, however, is the psychologic atmosphere engendered by the adults in the school and the adequacy of insight and training which they bring to this highly specialized task. This psychologic atmosphere consists of certain basic attitudes such as the acceptance of the child as a person rather than the censorship of his behavior, interest in ascertaining the motives behind his behavior, awareness of the back-and-forth nature of growth, and facility to nourish the first signs of independence without rejecting the child's lingering need to be supported and protected. These general attitudes determine the quality of the experience which the child derives from his activities. They underly the specific techniques which the teacher uses in connection with various aspects of the program.

Typically, the young child makes a physical-motor attack on the things in his world, sometimes through manipulating small objects, at other times through putting his large muscles or his whole body into vigorous motion and action. The nursery school is set up to provide ample, varied opportunity for the child to enjoy his physical vigor and, incidentally, to learn the nature of the physical objects in his surroundings. Slides, parallel bars and ladders, jungle gyms, see-saws, wagons, tricycles, scooters, large hollow wooden blocks, kegs, and brooms are part of the standard equipment, located usually outdoors, which is an essential prerequisite for adequate nursery school housing. A group of young children in contact with these objects spontaneously engages in a repetitive round of sliding, swinging, climbing, hanging, balancing, rolling, steering, heaving, pushing, stacking, and dragging. The benefits to development of muscular strength are obvious. There are, in addition, less obvious but more significant psychologic values. Instructions and restrictions are minimal, and limited to safety needs: the child is thus left free to explore, to experiment, to invent, and to discover. He is free from the host of prohibitions imposed upon him when he lets loose his most active impulses at home. In the course of physical activity, he encounters and comprehends more and more complex concepts of physicospatial relationships, "high and low," weight and pressure, wheel and axle, hoisting, leverage, etc. He is free from influences to use things as manufacturers conceive them, or as seem fascinating to his father. The child, then, has not only the pleasure of varied physical activity but also the delight of

making independent discoveries and the experience of impressing his own individual pattern on the environment.

In giving the children wide opportunity for action and expression and a minimum of prescribed instructions, the nursery school faces and takes certain specific responsibilities. Planning for space, equipment, and materials has to weigh carefully differences in age and capacity at different levels of the nursery years. Otherwise, the possibilities for accident and frustration are too great. No matter how carefully planned, there will be in any group of children incidents of reluctance, fears, frustrations, and of minor injuries. These themselves may constitute growth experiences when the child can feel confident that the teacher is competent to care for his injury and will express sympathy for his pain, that she will gladly stand by when he is slowly getting up his courage to step up to the highest rung, that she will be at hand to help undo the terrible tangle of rope that keeps the wheels from going around, that she will not make him feel he is a coward because he does not like to swing as high as the others do.

There is another kind of material which is provided plentifully for the children's spontaneous creative uses. This consists of colored paints, crayons, plenty of blank paper, building blocks, scraps of cloth, finger paints, modeling clay, anything, in short, which the child can manipulate, mould, or combine according to his own ideas. Left to his own devices, again with only a few restrictions as to ways in which materials may not be used, the child is free to enjoy the pattern of color which he devises or the structure of blocks which he erects. The opportunity to create according to his own impulse has several kinds of value to the growing child. In his private, independent experiences with color, design, or construction, the child is establishing himself as an individual capable of original creation; this is a process that is basic to his healthy ego development.

Through creative expression he can also release some of the pent-up, intense feeling generated in the course of his everyday life as a relatively helpless child in a world of powerful, all-knowing adults. In recent years, the value of free creative expression for young children has been clearly recognized since studies of their free products have demonstrated a detailed and close relation to the emotional ebb and flow of their lives. To assure these psychologic benefits to the child, more than the materials for creative expression are required. The teacher needs to be sensitive and appreciative of the children's products in terms of what the experience means to them. She does not apply extraneous standards of neatness, correctness, or photographic resemblance. She accepts the products as she does the child, careful not to impose adult criteria where they do not belong.

VALUE OF SOCIAL CONTACTS AND PLAY

It is not usually for these values, however important we may consider them to the child's developing individuality, that nursery schools are sought out by parents. It is more likely to be in search of companionship for a child who is lonely or bored, and therefore troublesome. Opportunities for playing and living together in nursery school are directly and deeply exhilarating, and the

children's joy is often ecstatic in quality. Besides this direct pleasure in social contacts with other children the young child in nursery school has a chance to widen his sphere of identification. He now belongs not only to the family into which he was born but to his school, a social group outside the home, and he is gradually initiated into the complicated social process by which individuals maintain themselves as acceptable and wanted members of social groups. Slowly he learns the mores of the nursery group: how to wait turns, the need to surrender what one does not use, how to settle conflicts by agreement and arrangement rather than fists, how to adjust his impulses to the requirements of the social situation.

He can count on the teacher to find an imaginative and just solution for the struggles, to exact no greater yielding of his own impulses than is suitable and healthy for his age and temperament, to be patient in repeated explanations and reminders, to join herself, from time to time, in the deeper experiences of kinship.

The children's life together in a nursery school constitutes primarily a life of play. In a spontaneous flow of ideas and acts, they play out dramatically the salient experiences of their lives, weaving the sequence as they go, shifting roles and changing scene without too much regard for the demands of logic and reality. This free dramatic play serves a variety of functions. Real experience is deepened and clarified as it is lived through dramatically over and over again. Much of the play however is symbolic in character or has symbolic elements through which the child unconsciously expresses anxieties, fears, wishes that he cannot deal with directly. The value of play in connection with emotional disturbance is being demonstrated currently in the growing use of play therapy as a technique for working with deeply disturbed children.

The teacher maintains an apparently passive role in relation to the children's dramatic play although she may become a participant on occasion by invitation. Her role, however, is not as passive as it appears on the surface. From her observations of the children's play she is guided in her dealings with individual children and their special problems. She also senses when the children as a group are ready for more extended experiences. The play of the children emerges in large measure from their experiences as members of families. It is also constantly nourished by the teacher's carefully planned program of trips into the neighborhood, reading of stories, and discussions of common experiences through which she develops the children's sensitive awareness and understanding of the world around them.

Briefly, one might summarize the values of nursery school experience which have been referred to so far by saying that they enrich the life of the young child, bringing to greater fulfillment the impulses which are natural to him at this stage of his development. Further, it has been indicated how important are the attitudes surrounding these experiences in relation to his growing sense of ego, his extended kinship feelings beyond the limits of home and family, the development of his creative and expressive capacities, his confidence in his own ability to discover, invent, and solve problems, his indirect resolution of emotional problems through symbolized dramatic play.

DISCIPLINE IN THE NURSERY SCHOOL

In the nursery school, then, he finds stimulation, understanding, heightened pleasures, and a great measure of freedom to grow through untrammeled expression of his feelings and interests. Just as vital to his total growth is his experience with control and authority. A child's mental health is conditional not only upon being loved, accepted, and protected but also upon having reasonable limits put upon his behavior, upon being stopped from carrying to excess some of his impulses (to be aggressive, for instance) and upon being able to accept certain decisions which must be made for him and cannot always be comprehensible to him. One of the goals of the nursery school is to give the child experience with temperate authority in contrast to the absolutism that was formerly characteristic of relations between adults and children.

In application, the concept of temperate authority refers to concrete ways of dealing with children. Severe punishments such as hitting, shaming, ridiculing, frightening are never visited upon the child. The teacher does not attempt to overpower him. Instead she makes an effort, as far as feasible, to let him know the reasons for what is expected, what is restricted, and what is not permitted. She tries to diffuse authority by having her student teachers and assistants share it and by having some of it implicit in the way she arranges schedules and programs until the children come to see what the situation requires. In exerting authority, it is the behavior which she censors and rejects, not the child. The child, in accepting this kind of discipline and authority, is neither humiliated nor demeaned. The value of experiencing authority of this kind while basic personality is still in formation extends beyond the sphere of the mental health of the child. It constitutes a psychologic bulwark for a democratic society.

In the development of these goals and practices during the last thirty or forty years the nursery school has been part of a larger educational movement usually referred to as progressive education. The progressive school has outlived its early experimental period and, we trust, is fast outliving some of the misconceptions concerning its practices and intentions. The concepts of fulfillment of the individual, the importance of motivation as a basis for efficient learning, of freedom without license, of learning through activity and direct experience, are only some of the tenets which are being absorbed currently into the practices of all modern schools, both public and private. The term "progressive" no longer refers to a small group of pioneer institutions. In fact, as a term, it is used less and less as its basic ideas are becoming the criteria by which we judge all good schools.

The attitudes concerning growth, freedom, and discipline, which have been attributed to teachers in nursery schools in the foregoing sections, are coming to be more and more characteristic of the relationships between parents and children. The question might be asked whether this does not make the nursery school experience superfluous. Certain features of nursery school are distinct from those of the home. For the sake of the child's wholesome growth as a psychologically independent individual there is great value in his realizing as early and as deeply as possible that the world outside the home and family holds

a full measure of warmth and security, great possibilities for pleasure and accomplishment. For some of the specific problems of his emotional development the nursery school has a distinct contribution to make just because his teachers, though intimate and close to him, are not as emotionally involved with him as are his parents, because there are children to enjoy with whom he does not have to work out sibling relationships, because the stage can be set for his childish interests and activities without interfering with the needs and preferences of adult living. For many children there is healthy satisfaction, also, in the expanded opportunities for achieving skills that add to one's feelings of independence and, more than that, an emerging sense of having a life of one's own.

THE DIFFICULT CHILD

Briefly outlined, these are the values for *any* child which are inherent in good nursery school education.* For the children who have more than the usual share of difficulties in early childhood, the experience can have important therapeutic value. The training of the teacher equips her to observe the child and study his behavior in order to understand its meaning, to provide a program of interests, and to guide his relationships according to his special needs and problems.

The behavior of the child is only the first clue to his difficulty and the teacher can plan intelligently only when she has studied the child sufficiently to have a tentative hypothesis as to the causes underlying his behavior. For example, a child may behave with extreme diffidence and hesitation when he comes to school, for any number of different reasons. His shyness may be due to the fact that he has made very few close relations to adults outside of a small family circle, or that he had been dominated and directed by an older sibling and felt at a loss as to how to act independently, or that he comes from a family of people who are naturally slow-moving and quiet and consequently he finds the nursery school atmosphere overwhelming rather than exhilarating at first. He may not speak the language of the children in the group, literally or figuratively, or he may be by nature one of those people who warm up slowly to all new situations.

Relieving his shyness is not a straightaway problem. The teacher may need to keep him close by her side through the early days until, having found confidence in a close relation with the teacher, he gathers strength to try himself out in contacts with the children. She may try to discover some special interests or experiences that he has, through which she can help him become interesting to the group. A cracker, a piece of toast, an extra dessert can help to break the ice when words might fail. Some children need only to be left to their own devices and allowed to stand quietly watching without partaking. Others take avidly to using all the materials and objects and gain their ease through becoming familiar with what there is to do before they can plunge into

*Printed pamphlets and articles on all aspects of nursery school education are available through National Association of Nursery Education. Distribution Center, Rooseveit College, S. Michigan Ave., Chicago, Ill.: Association for Childhood Education, 1201 16th Street, Washing, D. C.: New York City Committee of Mental Hygiene, 105 East 22nd Street, New York, N. Y.: The Bank Street Schools, Division of Research and Publications, 69 Bank Street, New York, N. Y.

social contacts. In some instances the teacher may realize that only through working with the family will she be able to help a particular child over his reluctance to take part in the life of the group.

What is true generally for shy behavior is also true for aggressive behavior, for bullying or whimpering, or for cheating or stealing on older age levels. There are no ready formulae for how to deal with these children or with others who may be especially fearful, anxious, rebellious, or sluggish. The details of the techniques to be applied have to be arrived at after each child's problem is studied and understood in terms of his personality and his total life situation. The extent to which they will be successful will depend on the depth of insight, the imaginative skill, and the emotional maturity of the teacher herself.

In any case, it is important to remember that the behavior difficulties of children who attend nursery school are relieved not only because of the specific techniques which the trained teacher knows how to use but also because of certain qualities pervading the entire situation. Among the most important are the teacher's acceptance of the child as a person despite the difficulties he may cause and the relief of working through one's problems in a nonfamily setting. For all these reasons, nursery school experience can be a valuable therapeutic agent, when there are not too many and too serious factors in a child's total life-situation operating against healthy resolution of problems.

INDICATIONS FOR NURSERY SCHOOL ATTENDANCE

We may return to the question posed in the beginning of this discussion concerning the points to be considered in coming to a decision as to whether a child should go to nursery school. Not all nursery schools are set up or equipped, nor all teachers trained in a way to offer this experience to young children. For some children a less than perfect nursery school may still be of great benefit. There are children whose home situations cannot provide what they should have of minimum essentials—space to move about in freely, a period of outdoor play each day, things and experiences through which to develop their growing bodies and minds, children to play with, and an atmosphere in which to have fun and be happy. There are children whose mothers work and leave them poorly provided for. There are children of professional women left in the care of domestic servants. There are children of broken families. In cases such as these, the decision to send a child to nursery school, even one which may not be achieving the highest possible standards, must be made in practical terms, by weighing and considering what his alternative environment would be. For judgments of this kind to be made with fewest possible errors it is important that there should be more widespread knowledge and understanding of the basic principles of nursery school education.

Decision to send a child to nursery school is a matter of *when* as well as *if*. In educational circles there is doubt and disagreement as to whether the nursery school should be set up for 2-year-old children, even though a considerable number of good schools have had many years of successful work with children in this age group. The issue will be difficult to resolve since it is bound up with differences in individual rates of development. Some 2-year-olds seem

to thrive in the nursery school situation. These are the children who are developmentally ready for long periods of separation from home and family, whose verbal and muscular skills are far enough along to keep them from feeling overwhelmed, who have enough stability to be able to carry on their bodily functions in a strange setting without being too deeply disturbed, and who have already developed a need for continuous contacts with other children. However, for many, this transplanting constitutes considerable strain.

The experienced staff member of a nursery school, after an interview, a home visit, and a little time with the child, is usually able to predict what the 2-year-old's reaction will be. With these very young children, there is more need for hesitation and careful consideration than is true for the 3-year-old. However, at any level in early childhood, leaving home and going to school for the first time is a stirring, often a shaking, experience. Practice now dictates that this period of weaning from home should be cushioned for the child as much as circumstance permits. Mothers are persuaded to remain in school while the child is getting initiated and gradually becoming familiar and secure. In some cases, it is best for the child to stay only for short periods in the beginning and it may be a matter of weeks before he is ready to spend a full day and take the round of eating and sleeping away from home.

In concluding, it should be noted that the value of the nursery school to the child depends not only on how good the nursery school is or on how inadequate his home is, but also on the motive of the parents in sending the child to school. One mother may be motivated by her own feeling of inadequacy, another by the wish to provide the best possible care and still another by a desire to reduce her own responsibility to a minimum. These differing motives will affect the child's receptivity to the nursery school experience. Because of his knowledge of the mother's personality, the pediatrician is in a favorable position to take this factor into account when his advice is sought.

The Social Aspects of Medicine

THE EWING REPORT

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ON SEPT. 2, 1948, Federal Security Administrator Oscar R. Ewing submitted to the President a report entitled *The Nation's Health—A Ten Year Program.* This report was in response to a request of the President made in January of that year. In May, 1948, Mr. Ewing called together the National Health Assembly, reports of which have been presented in various journals and need not be discussed at this time. The Ewing report draws heavily upon the material from that assembly and the discussions of the various sections, following in large measures its recommendations but departing from them in some respects, particularly with regard to compulsory health insurance, about which the assembly took no definite stand. The report is long and cannot be condensed into a few pages; it is worthy of careful reading by all members of the medical profession for, in view of the recent election results, it is probable that it will form the basis for legislation introduced into the next Congress. I should like to review briefly its main provisions without agreement or disagreement except in a few instances, and then only in most general terms.

The report begins with a blunt statement of some of the deficiencies in our national health record and the importance of doing the "utmost to insure that all the people everywhere attain the highest possible level of health." It then states the types of services and care that are needed to attain this goal. As listed, they are (1) medical and dental care, (2) a healthful community, (3) a community clinic, (4) a community hospital, (5) a district hospital, (6) special hospitals, (7) a medical center, (8) coordination, and (9) a prepayment plan. Also listed are parallel needs of (1) rising standard of living, (2) better educational institutions, (3) increased benefits to the aged and disabled, (4) adequate housing, and (5) public education in relation to health. Attention is called to the difference between demand and need and the methods of measuring adequacy of providing for need in the field of health. With this background, the key problems to be met are: (1) manpower, (2) hospitals, (3) local organization, (4) research, and (5) individual cost of care.

There are two methods by which the nation may proceed to improve the health situation: to continue slowly, as has been done in the past, or "to strike out boldly but with careful planning to bring our health resources quickly into line with our national and individual needs." The author concludes "that more extensive and efficient nation-wide planning is the only effective way to accomplish a significant betterment in national health." The remainder of the report is concerned with an elaboration of the key problems mentioned above and the nationwide plan to solve the problems. The parts to be played by the Federal,

State and local communities are discussed and emphasis is placed upon the desirability of working from the community up, not from Washington down. Throughout the entire report there are many statistical statements, based upon surveys and reports, and some opinions based on personal observation. These will not all be accepted as exact in every detail, nor will one always agree with the inferences drawn from them, but, by and large, they present a true picture of conditions in the fields with which they are concerned. The cost of sickness and disability and the wisdom of investing money to prevent this loss are recorded as further arguments for the need of a national health program.

There is a full discussion of manpower, physicians, dentists, nurses and public health workers—and its importance to the health program. Attention is called to the uneven distribution of personnel and selective shortages in particular fields. This is in line with the material found in the Report of the Committee on the Costs of Medical Care made twenty years ago. It is estimated that there are only 80 per cent of the physicians needed and that at the present rate of increase there is no prospect of filling the gap. It is proposed to accelerate the increase by "expanding and establishing medical colleges and teaching hospitals" by the use of public funds. The difficulties in hospital finances are to be met also by assistance from the Federal Government, a beginning of which has been made through the Hospital and Survey Act of 1946.

There follows a presentation of the unequal chances for health, relating them primarily to differences in financial status and emphasizing the economic barriers to utilization of health resources and the delay in seeking medical care. The author concludes that unless this barrier is overcome "the Nation will continue to be seriously handicapped in its efforts toward better national health." He then quotes the conclusion of The National Health Assembly's Section on Medical Care, that "the principle of contributory health insurance should be the basic method of financing medical care for the large majority of the American people."

The discussion on voluntary insurance plans calls attention to the good work which they have done and points out the obvious shortcomings, incomplete coverage and high cost. "The people who need health insurance most will not be able to get it under voluntary plans." The rest of the report presents the plan of a government insurance program.

The Government plan, as presented, envisions four phases:

Phase one:	"Federal legislation to settle the basic polices of a system of government insurance and to decide important details . . . and to provide a three-year 'tooling-up' period before the date on which insurance benefits are made available."
Phase two:	"The 'tooling-up' period during which procedures would be worked out cooperatively by professional groups, localities, States and the Federal Government."
Phase three:	"Operations begin."
Phase four:	"Expansion of services . . . until comprehensive services are available to everyone in the country."

Phase One, Legislation.—Provision would be made for statement of objectives, coverage, premiums, benefits, guarantees to insured persons, professional freedoms, benefits for rural people, education and research, state and local administration, allocation of funds, Federal administration, and collections. In the discussion of *Professional Freedoms,* the statement reads:

> "The law should give . . . explicit guarantees to the members of the professions who provide services, including the right to participate in the plan or not, to act individually or in groups, to accept or reject patients who choose them, to retain control of profession aspects of professional service, to choose the method of payment for services rendered, to negotiate rates or amounts of payment and other matters through representatives of their own choosing, to make complaints or appeals before appropriately constituted committees, and to turn to the courts for review of administrative decisions. Such guarantees would preserve the essential freedoms of the professions and assure that they could not be 'regimented' by administrative officers."

The suggestions in relation to the other matters are quite specific but will not necessarily be embodied in the legislation which may be introduced into the Congress. Discussion of them may well wait until such time as a bill is presented for hearings and enactment.

Phase Three, Operations.—It is estimated that 60 per cent of the population would be covered by the plan at its inception, with the ultimate goal of 100 per cent. The basic services, physicians, hospitals, expensive medicines, and appliances, would cost probably 3 per cent of annual earnings up to $4,800 a year, divided between subscriber and employer. When other services are added, an additional 1 per cent would be needed.

It is stated that the plan as outlined would make five fundamental contributions to better health:

> "1. It would largely solve the individual's problem of paying for medical care, and thus help encourage prompt care and preventive treatment.
>
> "2. Because it creates a stable and assured financial basis for health services, it will generate effective demand and assure the fastest possible increase in our supply of medical manpower, health facilities and other essentials in all parts of the country.
>
> "3. Because insurance will pay for a patient's needs, doctors will be free to practice the highest quality of scientific medicine, uninhibited by the individual patient's ability to pay out of personal income for all the diagnostic and treatment services, hospitalization and nursing care which professional judgment prescribes.
>
> "4. Because insurance will abolish most of the financial obstacles to receiving medical care and help equalize community purchasing power, it will reduce the present large disparities in distribution of manpower and health facilities between lower-income areas and wealthier districts.
>
> "5. Because national health insurance will furnish a new and badly needed opportunity for co-ordination of all community and regional personnel and facilities, it will help build a more effective organization for providing the best in prevention, diagnosis and treatment."

There is next a section devoted to a consideration of six objections to Government health insurance:

> "Briefly, the six arguments are these: (1) That Government health insurance is socialized or state medicine, (2) that it is compulsory, (3) that it would be highly centralized and would concentrate too much power in Federal Government, (4) that there are not sufficient personnel and facilities to make it effective, (5) that it would cost too much, and (6) that it would open the way to over-use and other abuses and would lower the quality of medical services."

Each one of these objections is met by factual material and opinions, leading the author to conclude that the adverse arguments are not conclusive, and that, in fact, the suggested plan effectively overcomes the difficulties about which the opponents are particularly apprehensive. This portion of the report ends with this sentence, "I, therefore, recommend that the President continue to urge upon the Congress the earliest possible enactment of government health insurance in some such terms as outlined in this report."

There are four chapters dealing, respectively, with mental health, the aging population and chronic diseases, the handicapped, and child health. Methods for improving present conditions and the part to be played by Government are discussed. There is nothing strikingly new with regard to child health. In general, it is advocated that the present services be expanded along present lines but made inclusive in those areas which are particularly backward.

The final chapter deals with community action. This is a clear presentation of the advantages of "effective team work for the welfare of the entire community." It outlines the generally accepted plan of rural clinics, local hospitals with district and base hospital communication. It calls attention to the importance of the medical school center and the advantages of group practice. The report ends with a plea for community action and team work:

> "If the people will get together—professional workers and public representatives alike—in citizen health councils throughout the country, we will have the satisfaction of proving not only that health is everybody's business but that it is good business, essential business, and successful business."

Comments on Current Literature

CHLOROMYCETIN

THE antibiotic, Chloromycetin, obtained from strains of Streptomyces which were isolated from soil and compost,[1-3] is known to inhibit a wide variety of gram-positive and gram-negative microorganisms. These include *Bacillus subtilis, Staphylococcus aureus, Brucella abortus, Escherichia coli, Klebsiella pneumoniae, Salmonella schottmülleri* and *Shigella paradysenteriae.*

In addition to its effect on bacteria, Chloromycetin was shown to have a beneficial effect when administered to mice and to embryonated hen's eggs infected with a number of rickettsial agents or with viruses of the psittacosis-lymphogranuloma venereum group.[4] Noninfected control mice and embryonated eggs which received amounts of Chloromycetin comparable to the maxima used in the experimental series remain unaffected, indicating low toxicity of the drug. On the basis of early observations concerning low toxicity, ready absorption from the alimentary tract, and beneficial effect even when administered late in the experimental infection, Smadel and his associates[4] suggested that Chloromycetin might prove valuable in the treatment of patients. Subsequent clinical experiences have borne out their suggestion.

A preliminary study[5] was made on a group of volunteers who received maximum single or repeated oral doses, and in no instance were toxic manifestations observed during or after administration. Following this preliminary work on normal volunteers, five patients with typhus were treated with the same oral doses.[6] Improvement was noted in all five patients with fall in pulse rate and body temperature, and no toxic effects were observed. Subsequent opportunity for more extensive therapeutic testing[7] was afforded in cooperation with the Malaya Institute of Medical Research during an outbreak of scrub typhus at Kuala Lumpur. Twenty-five hospitalized patients were treated with Chloromycetin and at the same time twelve untreated hospitalized patients were observed. The results of these observations indicated that Chloromycetin had a favorable effect on the clinical course of scrub typhus.

In a recent issue of *Annals of Internal Medicine,*[8] Pincoffs, Guy, Lister, Woodward, and Smadel report their experience with Chloromycetin in the treatment of Rocky Mountain spotted fever. Fifteen cases confirmed later by laboratory findings were treated. Ten of these patients were under 16 years of age (2 to 16) and five were above this age (17 to 64). The dosage regime was empirical. The initial dose, which was administered per os in two or three parts at approximately one-hour intervals, ranged from 50 to 75 mg. per kilogram estimated body weight; in one instance 128 mg. per kilogram estimated body weight was given. After the initial dosage Chloromycetin was administered at three-hour intervals, 0.25 Gm. every three hours for children under 16 years of age, and 0.5 Gm. for those over 16 years of age.

While some improvement was noted during the first twenty-four hours of treatment, striking amelioration of the clinical manifestations was observed during the second day of therapy. "On the third day, in the majority of cases, the patient was plainly convalescent."[8] In all cases the temperature fell to normal levels within seventy-six hours after the initial dose. Other than occasional vomiting following the initial dose, no toxic manifestations were observed.

In the course of the investigations on scrub typhus in Malaya, the authors encountered numerous cases of typhoid fever which is endemic in this area, and which occurs in a severe form, the febrile course running from six to eight weeks. These cases offered opportunity for testing the value of Chloromycetin in this important enteric disease.[9] Diagnosis in the ten cases treated was confirmed by blood cultures positive for *Eberthella typhosa*. Beneficial effect of Chloromycetin was noted within the first twenty-four hours following administration in improved general condition of the patient and in lessened toxicity. The febrile course was reduced considerably. While the optimum schedule for the administration of the drug in typhoid fever remains to be determined, in this series the initial dose in each case was 50 mg. per kilogram of estimated body weight, then 0.25 Gm. administered every two hours until the temperature was normal, and 0.25 Gm. every three to four hours during the first five days of normal temperature. The total dosage averaged 19.1 Gm. over a period of 8.1 days. No clinical evidence of toxicity was observed.

The striking effect of Chloromycetin on the clinical course of epidemic typhus, scrub typhus, Rocky Mountain spotted fever, and typhoid fever indicates that this antibiotic is to date the most effective therapeutic agent available in the treatment of these diseases. The apparent lack of toxicity, the ease of administration by the oral route, the beneficial effect even when administered relatively late in the disease, and the broad coverage of therapeutic effectiveness make this drug an outstanding addition to the medical armamentarium.

RUSSELL J. BLATTNER

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News and Notes

Dr. Bert I. Beverly of Oak Park, Ill., died Sept. 27, 1948. He was associate professor of pediatrics at the University of Illinois and for years had been one of the leaders in the field of child psychiatry.

Dr. John D. Lyttle of Los Angeles died Nov. 26, 1948. Formerly associated with the Columbia Medical Center and Babies Hospital in New York, he went to Los Angeles in 1944 where he was Medical Director of the Children's Hospital and professor of pediatrics at the Medical School of the University of Southern California.

At the annual meeting of the **American Academy of Pediatrics,** held in Atlantic City Nov. 19 to 22, Dr. Warren R. Sisson of Boston was elected President for 1948-1949, and Dr. Edward B. Shaw of San Francisco, President-Elect.

Dr. Milton J. Senn, professor of pediatrics in psychiatry at the Institute of Child Development at Cornell Medical College, has been appointed Sterling professor of pediatrics and psychiatry at Yale. He will be director of the new Yale University Child Study Center which will include the Yale Clinic of Child Development.

Dr. Hunter H. Comly has been appointed assistant professor of pediatrics in the Department of Psychiatry at the University of Iowa College of Medicine.

The **National Foundation for Infantile Paralysis** is offering postgraduate fellowships for research, and in public health and physical medicine, for physicians who wish to enter these special fields. The research fellowships are available in pediatrics, virology, orthopedic surgery, epidemiology, and neurology. Physicians who have served a minimum of two years' training on the residency level in the specialized field are eligible. Candidates must present an appropriate program of study and investigation. From a financial standpoint, awards are based on the individual qualifications and need of each applicant, and will include a monthly allowance, laboratory and other expenses deemed advisable for carrying out the program. Selection of candidates will be made by committees composed of qualified scientists. Detailed information may be obtained from the Foundation, 120 Broadway, New York 5, N. Y.

The **Maurice Lamm Blatt Memorial Fund** wishes to announce a prize of $250.00 to be given for a piece of original research work done by an Intern or Resident of the Cook County Hospital or a former Intern or Resident who has been out of the Hospital for a period of not more than five years. All communications should be addressed to the Maurice Lamm Blatt Memorial Fund, Children's Division, Cook County Hospital.

Dr. Stanley Gibson is retiring on Jan. 1, 1949, as Chief of Staff of the Children's Memorial Hospital in Chicago, having attained the normal retirement age during the current year, but will continue on the medical staff as consulting cardiologist. Dr. John A. Bigler has been appointed Chief of Staff of the Hospital, effective Jan. 1, 1949.

At the annual meeting of the National Committee for Mental Hygiene in November, the Lasker Award in mental health was given to Dr. C. A. Aldrich of Rochester, Minn., for outstanding accomplishments in the education of physicians in the psychological aspects of the practice of medicine.

Book Reviews

Pediatric Nursing. Gladys S. Benz, R.N., M.A., St. Louis, 1948, The C. V. Mosby Company, 638 pages. Price $4.00.

This new text on pediatric nursing is in many respects the most satisfactory discussion of the subject that has appeared. The author has had a broad experience of nursing and instruction in children's hospitals in Minneapolis, Chicago, St. Louis, and Albany, which the text reflects. Perhaps one of the reasons we like it so much is that it is really a text on pediatric nursing and not an abridged text on pediatrics for nurses like some of the books in the field. For example, the excellently illustrated discussion of infant feeding gives in detail the preparation of the formula and the technique of the milk laboratory in the hospital, but does not go into the detail of prescribing the formula. A most unusual comprehensive bibliography is attached to each section for the nurse who for some reason or other desires to go more fully into the subject. The author has also prepared a separate "Teacher's Guide" for use by the instructor in pediatric nursing. The style is pleasant and easy reading, and the text is obviously the work of the author and not something just copied and cut down.

B. S. V.

Malaria in Kindesalter (Malaria in Childhood). Albert Eckstein, Basel and New York, 1946, S. Karger, 119 pages. Price Swiss frs. 15.

This book gives a rather complete survey of the prophylaxis, clinical manifestations, and therapeutics of malaria in childhood, of which the author in his present position in Ankara obtained an enormous experience within a relatively small number of years. The extensive discussion of many complications of malaria in childhood, all illustrated by a short report of clinical cases, will be highly appreciated by the reader, as will be the chapter on the mutual influence of malaria and other diseases in childhood (in the author's region especially noma). It is to be regretted that the references cited by the author are restricted with the result that some recent fundamental literature and findings on the subject are lacking.

v. C.

1948 Year Book of Pediatrics. Edited by Henry C. Poncher, M.D., Chicago, Year Book Publishers, Inc., 541 pages. Price $4.50.

The annual "Year Book" of pediatrics has a new editor. There is an excellent selection of material from the pediatric literature of the world with emphasis on subjects of interest and value to the general practitioner for whom the book is primarily intended. The abstracts are clear and well written. The editor has occasionally injected comments which the reviewer feels could well be extended in subsequent volumes as it is pertinent and to the point. This year's volume is decidedly better than the last few volumes, due in part no doubt to the hospitals and clinics getting back to a normal productivity after the personnel and teaching problems of the war.

Your Baby. Gladys D. Shultz and Lee Forrest Hill, M.D., New York, 1948, Doubleday and Company, Inc., 278 pages. Price $3.50.

This is the most elaborate book on infant care that has appeared. It is a large book more suited for the table than for the shelf, and the format and illustrations are most attractive. The authors are a well-known editor of women's magazines who is obviously responsible for the style of the text, collaborating with a well-known pediatrician who is responsible for the text being medically sound and in keeping with present-day thought and trends. The last forty pages contain elaborate records to be kept up by the mother. By experience we know they will be started and soon discontinued. In this specific case we hope that some of the records, such as those on sex, bright sayings, parent's opinions as to the child's personality, and the like, will never be started, as a grown child reading over the record would probably develop a loathing for the parent. We can prophesy a tremendous sale of the book as a "gift" to the mother with her first baby.

Hospital Trends and Developments (1940-1946). Edited by A. C. Bachmeyer, M.D., and Gerhard Hartman, Ph.D., New York, 1948, The Commonwealth Fund, 819 pages. Price $5.50.

This book is an extremely useful compilation for hospital administrators, students in hospital administration, medical administrative officers, deans of medical schools, and other clinical department heads who have a definite interest in hospitals.

It is a successor to "The Hospital in Modern Society" which covered a period in hospital literature between 1930 and 1940. The present volume deals with the years 1940 to 1946. There is little change, except in Part One. This section shows a very definite and new emphasis on preventive medicine and positive health, featuring such writers as Isadore S. Falk, V. M. Hoge, M.D., and Thomas Parran, M.D., of the Public Health Service. There are comments on the community hospital and public health by Ira V. Hiscock, Professor of Public Health at Yale, discussion on rural hospital and health facilities, and the latest health developments in foreign countries.

The contents of the book are well selected and reflect the condensed thinking of the most active leaders and administrators in the field of hospital service. In this compact volume almost the entire hospital field is so covered that the reader, by checking the contents, may find it a useful and handy index. Under the chapter on "Special Services," psychiatric care is featured under the authorship of Karl Menninger, M.D., and communicable diseases are given considerable space and discussion. For some reason, which is not known, pediatrics does not receive a special chapter, but is considered in the general approach in several articles. Also, the subject which relates to both pediatrics and psychiatry—the child guidance clinic—is not featured in chapter form. All in all, the book is an excellent one for people interested in hospitals and medical administration and should be available to medical, nursing, and social service staffs. It is clear that articles are chosen for their objective presentation of problems and their solution, and the editors have selected such articles with the idea of stimulating thought, regardless of the views of the editors themselves; in fact, some articles are in disagreement with their opinions.

F. R. BRADLEY

Therapy Through Interview. Stanley G. Law, New York, McGraw-Hill Book Company, Inc.

An essential part of psychiatric diagnosis and therapy is the interview with the patient. Dr. Law, a general practitioner for twelve years, describes the technique of interview which he has found most useful.

He calls attention to the three phases of therapy: resistance to the therapist; acceptance of help; separation from the therapist and independence. Knowing the stages through which the patient passes will help the beginner to recognize progress in therapy. Dr. Law's technique through interview is to proceed as rapidly as is consistent with the patient's attitude. He stresses the need to have the patient work out his own problems. Dr. Law leads him, pushes him, helps him to express his feelings and to make decisions but is careful not to influence him. He accepts his patient and his aggressions from the start, and this frees him from his feelings of guilt. This done, half the battle is won.

The technique seems simple enough and, with real interest and some study, most physicians could undertake this kind of therapy although it is time-consuming for the interviews do not always go smoothly. Dr. Law stresses the importance of a mature personality in the therapist. He must be able to accept the changes which the patient desires in his personality and not build up a concept of what he wishes him to be as a result of the therapy.

The book is simply, often entertainingly, written. The language is clear, and terms, which may have doubtful meaning to the general practitioner, are avoided. The case histories and explanations are so concrete that it is easy to identify oneself with the doctor interviewing the patient.

Dr. Law clarifies a form of therapy used both unconsciously and consciously by many physicians in the handling of emotional difficulties in their patients. He presents a clear-cut picture of the mode of approach to the problems. Best of all, because of his prompt and good results in so many cases, he will give confidence to the physician who would like to help his own patients rather than sending them elsewhere for psychiatric treatment.

RUTH BAKWIN

Editor's Column

DIAGNOSIS OF CONGENITAL MALFORMATIONS OF THE HEART

AMONG those in the audience at the recent meeting of the American Academy of Pediatrics in Atlantic City who listened to the Symposium on Congenital Heart Disease by Gibson, Taussig, Bing, Keith, Blalock, and Potts, must have been many whose thoughts, spoken or unspoken, reverted back to the time only a few years ago when the best that could be done in congenital anomalies of the heart was an attempt to identify the lesion for purposes of prognosis relative to disability and life expectancy. By comparison, the methods employed today in the diagnosis and surgical management of malformations of the heart and great vessels are little short of miraculous. They represent a triumph of medical science which deserves documentation among the great advances of all time.

Three rather distinct methods have evolved for the study and recognition of congenital heart defects. Demonstration that certain abnormalities are susceptible to surgical attack has, of course, stimulated research in all three fields. Children with congenital heart disease are of common occurrence in all pediatric clinics, and the problem of weeding out the operable from the inoperable has to be met constantly. Hence, most pediatric hospitals sooner or later will have to consider the question of the method or methods of study which shall be adopted in their particular institution, even though it be for the purpose of selecting cases to be sent on to the center whose facilities include those of the cardiac surgeon.

Angiocardiography has become an established diagnostic procedure. Castellanos began his studies in this technique as early as 1936. Demonstration of its value in the cyanotic group of infants and children by intravenous injection of Diodrast is clearly set forth in an article in the November issue of THE JOURNAL OF PEDIATRICS by Carson, Burford, Scott, and Goodfriend, and in the December issue of the JOURNAL, Carson and Burford have shown the remarkable clarity with which coarctation of the aorta and patency of the ductus arteriosus can be roentgenographically visualized following retroarterial injection of Diodrast into the left common carotid artery. Although these techniques possess obvious advantages, especially in borderline or obscure cases, nevertheless it must be emphasized that they are highly technical procedures requiring a team of experts, automatized radiographic equipment, and a special, rather expensive hospital setup. Nor are they entirely devoid of danger, since an occasional death has occurred even in the hands of the most experienced. It is conceivable that eventually angiocardiography may become as safe for properly selected cases as is intravenous pyelography, and that roentgenologists and clinicians will become equally adept in technical performance and interpretation of roentgenograms. But until that time comes, if it does, it would seem

that the nationwide needs of the children with congenital heart disease might best be met by a limited number of strategically located units whose personnel includes individuals with special training and experience in this particular diagnostic approach.

Almost the same comments could be made about catheterization of the chambers of the heart as a method of diagnosis in congenital heart disease as were made about angiocardiography. It, too, is a highly technical procedure, but perhaps involves less risk to the patient.

Taussig has stressed that the majority of malformations of the heart can be accurately diagnosed by methods which do not require either catheterization or angiocardiography. In her excellent book she states that "accurate diagnosis of the nature of the malformation is usually made possible by the information derived from physical examination, x-ray, fluoroscopy, and electrocardiography." Obviously, this method has the advantages that it is completely safe for the child and that it is available to every clinician. Many children in Taussig's clinic, and in others, have had the correctness of a diagnosis arrived at by the studies enumerated above confirmed at operation. It will take time before final evaluation can be made as to the advantages of the additional information derived from catheterization or angiocardiography in the diagnosis and surgical management of congenital heart disease. There is no question but that all three methods should and will be continued. But the point of these remarks is that, perhaps, the more technical procedures are best carried on in large centers by experienced workers.

L. F. H.

THE EWING REPORT

In an editorial in the December issue attention was called to the importance and significance of the Ewing report on the nation's health. Dr. Richard Smith has kindly abstracted the report for the JOURNAL readers which appears on page 120 of this issue. The JOURNAL is taking no position pro or con. It is simply that we feel the report is of so much importance that its content should be known by every physician.

B. S. V.